Development of a Concise Synthesis of Ouabagenin and Hydroxylated Corticosteroid Analogs

Hans Renata,[†] Qianghui Zhou,[†] Georg Dünstl,[‡] Jakob Felding,[‡] Rohan R. Merchant, Chien-Hung Yeh,

*and Phil S. Baran**

Contribution from the Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla,

California 92037, United States, and Front End Innovation, LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark

SUPPLEMENTARY MATERIAL – PART 1 – PROCEDURES

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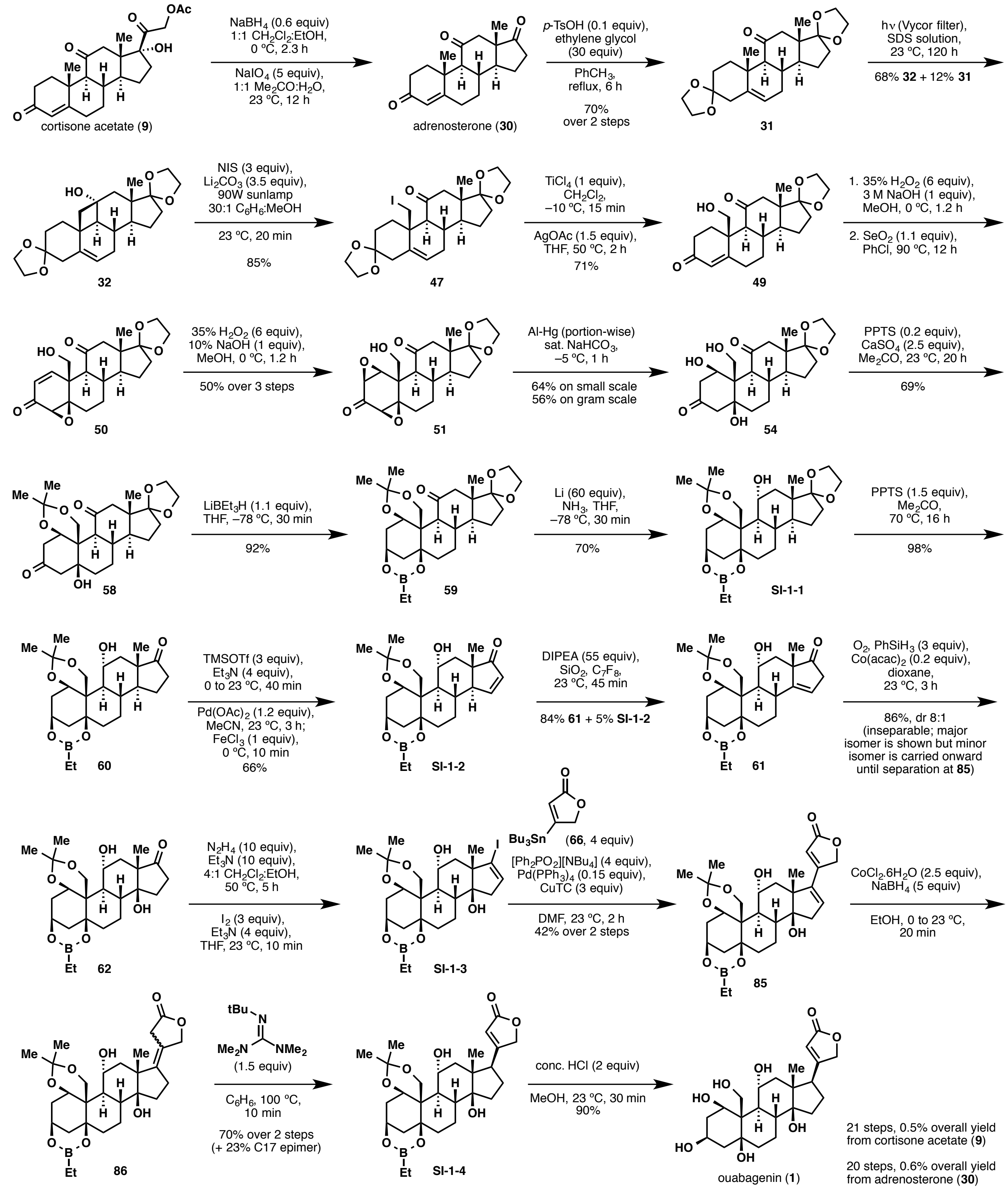
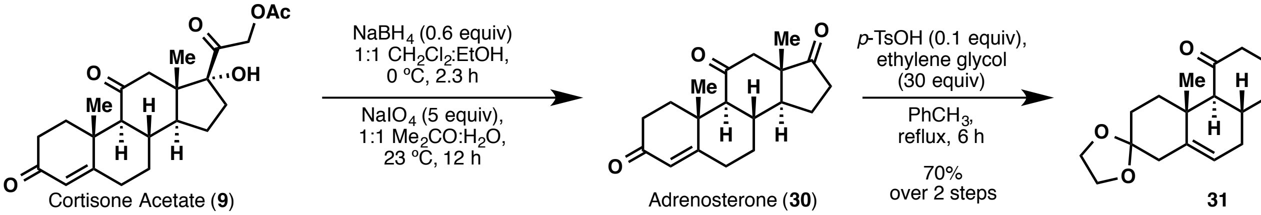
General procedures. All reactions were carried out under a nitrogen atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), toluene (PhMe), *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF), methanol (MeOH) and triethylamine (Et_3N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate ($KMnO_4$), and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ @ 7.26 ppm ^1H NMR, 77.16 ppm ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time of flight reflectron experiments. IR spectra were recorded on a Perkin Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected.

Scheme S1. Final working scheme for the synthesis of ouabagenin (**1**).



Experimental Procedures Part 1

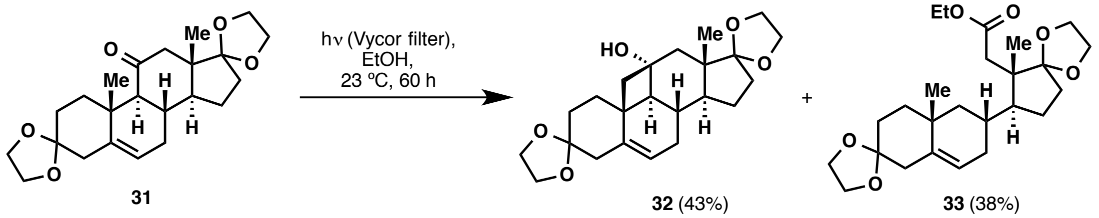


Adrenosterone (30): To a solution of cortisone acetate (**9**; 20.0 g, 49.7 mmol) in 1:1 CH_2Cl_2:EtOH (320 mL) at 0 °C was added $NaBH_4$ (564 mg, 14.91 mmol, 0.3 equiv). After 45 min, another portion of $NaBH_4$ (282 mg) was added. After another 45 min, one final portion of $NaBH_4$ (282 mg) was added. A mixture of acetone:water (1:1, 160 mL) was added after another 45 min and the mixture was warmed to ambient temperature, followed by addition of $NaIO_4$ (53.2 g, 248.5 mmol, 5 equiv) over 5 min. The resulting white slurry was stirred overnight, filtered through Celite® and evaporated until the majority of CH_2Cl_2, EtOH and acetone had been removed to provide a suspension of off-white solid in water. Water (ca. 400 mL) was added to this mixture. Following vacuum filtration and washing with Et_2O (300 mL), an off-white solid (12.8 g, 86%) was collected, which was sufficiently pure for the next step.

Ketal 31: To a solution of adrenosterone (**30**; 12.8 g, 42.6 mmol) in toluene (530 mL) was added ethylene glycol (70 mL) and *p*-TsOH·H_2O (0.81 g, 4.26 mmol, 0.1 equiv). The reaction vessel was incorporated into a standard Dean-Stark setup and immersed in an oil bath preheated to 140 °C and stirred vigorously. After 6 h, the reaction was lifted out of the oil bath and allowed to cool. The layers were allowed to settle and the ethylene glycol was separated from the organic layer; this was then neutralized with sat. aq. $NaHCO_3$ (100 mL) and the aqueous portion was extracted with EtOAc (3 x 100 mL). The organic portions were combined, washed with sat. aq. NaCl (150 mL), dried over $MgSO_4$ and concentrated. Recrystallization of the crude product by boiling in 10:1 Et_2O:EtOAc (ca. 450 mL), followed by cooling at 4 °C furnished the known ketal compound **31** (13.4 g, 81%) after three cycles.

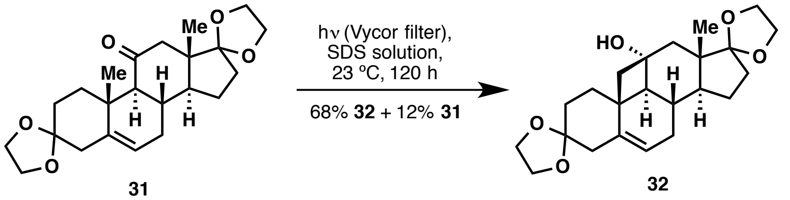
Cyclobutanol 32:

A. Photolysis in Ethanol



Diketal **31** (5.00 g, 12.87 mmol) was dissolved in dry EtOH (1.0 L), transferred to a photoreactor [ACE glass, 1 L jacketed reaction vessel (#7841) with quartz immersion well (#7854)] and purged with argon for 15 min, followed by irradiation using a 450W mercury Hanovia lamp through a vycor filter for 60 h. The solution was then poured into a round-bottom flask and concentrated *in vacuo*. The resulting oil was purified by column chromatography (1:4 to 3:2 EtOAc:hexanes) to give **33** (1.90 g, 38% yield) as a clear oil and **32** (2.15 g, 43% yield) as a white solid.

B. Solid-State Photolysis of Crystal Suspension



Crystals of diketal **31** (2.00 g, 5.15 mmol, grown as described in the ketalization procedure in the previous page) and sodium dodecyl sulfate (SDS) (1.0 g) were transferred to a photoreactor with quartz immersion well. Degassed water (1.0 L, purged with argon) was then added followed by irradiation using a 450W mercury Hanovia lamp through a vycor filter for 120 h. The mixture was poured into a separatory funnel and extracted with EtOAc (3 x 150 mL). The combined organic layers were then washed with brine (250 mL), dried over $MgSO_4$, filtered through a pad of silica to remove any remaining SDS and concentrated *in vacuo*. The resulting yellow oil was purified as described above to give recovered **31** (0.24 g, 12%) and **32** (1.36 g, 68%) as a white solid.

Physical state: white solid (m.p. 190 °C).

R_f = 0.34 (silica gel, 3:2 EtOAc:hexanes).

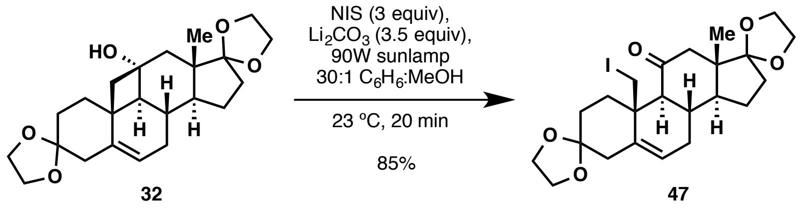
$[\alpha]_D = +14.8°$ (c = 1.0, CH_2Cl_2).

HRMS (*m/z*): calcd for $C_{23}H_{32}O_5$, $[M+H]^+$, 389.2322; found, 389.2303.

IR (film) ν_{max} = 3466, 2967, 2937, 2880, 1734, 1709, 1172, 1121, 1075, 978, 949.

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.61 (d, *J* = 6.8 Hz, 1 H), 4.02–3.71 (m, 8 H), 2.84 (dt, *J* = 13.4, 3.5 Hz, 1 H), 2.47 (d, *J* = 11.6 Hz, 1 H), 2.21–2.09 (m, 3 H), 2.04 (dd, *J* = 11.7, 4.9 Hz, 1 H), 1.94 (ddd, *J* = 14.6, 11.5, 3.3 Hz, 1 H), 1.87–1.77 (m, 2 H), 1.76–1.65 (m, 4 H), 1.61 (d, *J* = 14.0 Hz, 1 H), 1.58–1.25 (m, 5 H), 0.97 (s, 3 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 141.3, 125.9, 119.0, 109.6, 77.0, 65.1, 64.7, 64.5, 64.4, 57.3, 49.6, 45.0, 44.3, 42.6, 42.4, 41.8, 38.7, 34.7, 34.6, 32.1, 27.1, 20.8, 17.1.



Iodide 47: Cyclobutanol **32** (3.60 g, 9.26 mmol) was dissolved in toluene (180 mL, 0.05 M), followed by sequential addition of MeOH (6 mL), Li$_2$CO$_3$ (2.39 g, 32.41 mmol, 3.5 equiv) and NIS (6.25 g, 27.78 mmol) under Ar. The resulting suspension was irradiated with sunlamp (90 W, 6 inches from the walls of the flask) for 15 min. Irradiation was then halted and the crude mixture was washed with saturated aqueous Na$_2$S$_2$O$_3$ (75 mL) until colorless. The aqueous layer was back-extracted twice with EtOAc (2 x 125 mL) and the combined organic layers were washed with brine (50 mL), dried over MgSO$_4$ and concentrated *in vacuo*. The resulting yellow oil was used for the next step without further purification. This yellow oil could also be purified by silica gel chromatography (1:4 EtOAc:hexanes) to give pure **47** (4.77 g, 85%) as a white solid.

Physical state: white solid (decomp. 110–115 °C).

R$_f$ = 0.42 (silica gel, 2:3 EtOAc:hexanes).

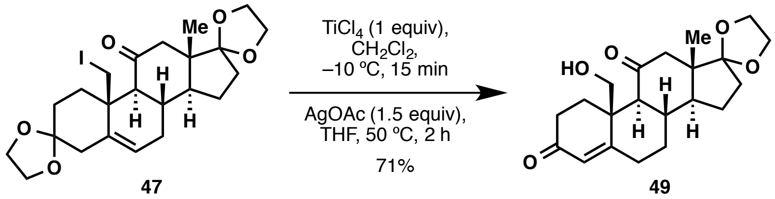
HRMS (*m/z*): calcd for C$_{23}$H$_{31}$IO$_5$, [M+H]$^+$, 515.1289; found, 515.1298.

[α]$_D$ = –23.6° (*c* = 0.5, CH$_2$Cl$_2$).

IR (film) ν_{max} = 2945, 2877, 1698, 1446, 1372, 1313, 1280, 1245, 1215, 1174, 1100, 1056.

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.74–5.33 (m, 1 H), 4.35 (d, *J* = 11.1 Hz, 1 H), 4.00–3.76 (m, 8 H), 3.62 (dd, *J* = 11.0, 1.4 Hz, 1 H), 2.83 (qd, *J* = 10.8, 5.2 Hz, 1 H), 2.62 (dd, *J* = 13.9, 4.5, 2.8 Hz, 1 H), 2.61 (dd, *J* = 13.6, 1.2 Hz, 1 H), 2.41 (dq, *J* = 14.1, 2.8 Hz, 1 H), 2.25 (td, *J* = 5.4, 2.7 Hz, 1 H), 2.16 (dd, *J* = 13.9, 2.4 Hz, 2 H), 2.09–2.00 (m, 2 H), 1.96–1.75 (m, 5 H), 1.62 (ddt, *J* = 14.3, 4.3, 2.8 Hz, 1 H), 1.47–1.32 (m, 2 H), 0.95 (s, 3 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 211.4, 137.9, 124.0, 118.0, 108.5, 65.5, 64.7, 64.6, 64.5, 60.8, 50.2, 50.0, 48.8, 41.6, 39.6, 35.6, 34.4, 33.7, 31.4, 31.1, 22.5, 15.9, 10.0.



Enone 49: Crude iodide **47** was dissolved in CH_2Cl_2 (180 mL). After cooling to –10 ºC, a solution of $TiCl_4$ in CH_2Cl_2 (1 M, 9.26 mL, 9.26 mmol) was added dropwise, at which point, the solution turned dark red. After 20 min, the reaction was quenched with sat. aq. $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 75 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

The resulting oil was dissolved in THF (180 mL), followed by sequential addition of H_2O (9 mL) and AgOAc (2.32 g, 13.89 mmol, 1.5 equiv). The resulting mixture was heated to 50 ºC for 2 h. The reaction was cooled to room temperature, diluted with EtOAc (75 mL), filtered through a pad of Celite® and concentrated *in vacuo*. The yellow oil was purified by silica gel chromatography (3:7 to 3:2 EtOAc:hexanes) to give enone **49** (2.00 g, 71%) as a white solid.

Physical state: white solid (m.p. 155–157 °C).

***R**$_f$* = 0.25 (silica gel, 3:2 EtOAc:hexanes).

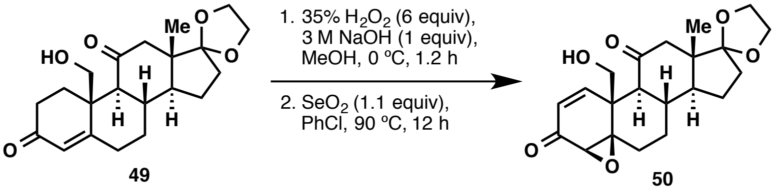
HRMS (*m/z*): calcd for $C_{21}H_{28}O_5$, $[M+H]^+$, 361.2009; found, 361.2000.

$[\alpha]_D$ = +106° (*c* = 1.0, CH_2Cl_2).

IR (film) ν_{max}: 3346, 2974, 2935, 2894, 1698, 1664, 1617, 1169, 1157, 1047, 1041.

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.79 (s, 1 H), 4.17 (dd, *J* = 11.7, 2.3 Hz, 1 H), 4.03–3.77 (m, 4 H), 3.74 (dd, *J* = 11.7, 8.7 Hz, 1 H), 2.84–2.71 (m, 2 H), 2.84–2.71 (m, 2H), 2.38–2.20 (m, 4 H), 2.14 (d, *J* = 11.8 Hz, 1 H), 2.10–1.88 (m, 5 H), 1.86–1.77 (m, 1 H), 1.58 (td, *J* = 13.9, 4.4 Hz, 1 H), 1.38 (tt, *J* = 12.1, 5.9 Hz, 1 H), 1.31–1.15 (m, 1H), 0.84 (s, 3 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 214.0, 199.7, 165.5, 125.6, 117.4, 65.6, 64.7, 64.3, 64.3, 50.1, 49.9, 49.5, 43.4, 38.4, 34.4, 34.4, 32.9, 31.7, 31.4, 22.1, 14.9.



Enone 50: Enone alcohol **49** (2.00 g, 5.55 mmol) was dissolved in MeOH (56 mL, 0.1 M) and cooled to 0 ºC. 10% NaOH aqueous solution (2.0 mL, 1.0 equiv) was added, followed by 35% H_2O_2 (2.84 mL, 6.0 equiv, added in 3 portions in 25 min intervals). The reaction was diluted with EtOAc (75 mL) and quenched with sat. aq. $Na_2S_2O_3$ (75 mL) at 0 ºC. After warming to room temperature, H_2O was added to dissolve the white precipitate that was formed upon quenching. The aqueous layer was extracted with EtOAc (2 x 125 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting off-white foam was used for the next step without further purification.

The above epoxide (epoxidation yield was assumed to be quantitative) was dissolved in PhCl (56 mL), followed by the addition of SeO_2 (678 mg, 6.11 mmol, 1.1 equiv) and heating to 90 ºC for 12 h. The reaction was cooled to room temperature and neutralized with solid $NaHCO_3$ (1.90 g), followed by $MgSO_4$ (2.40 g). The dark brown suspension thus obtained was filtered through a pad of Celite® and concentrated *in vacuo*. The resulting brown oil (compound **50**) was used for the next step without further purification.

Physical state: foam.

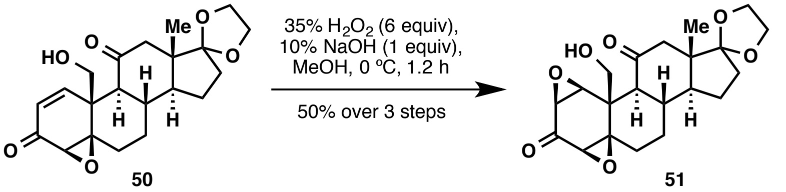
R_f = 0.38 (silica gel, 3:2 EtOAc:hexanes).

HRMS (*m*/*z*): calcd for $C_{21}H_{26}O_6$, $[M+H]^+$, 375.1802; found, 375.1799.

IR (film) ν_{max}: 3470, 2946, 2880, 1703, 1680, 1167, 1099, 1057, 1039, 915, 833, 732.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.30 (d, *J* = 10.8 Hz, 1 H), 5.94 (dd, *J* = 10.8, 2.0 Hz, 1 H), 4.43 (dd, *J* = 11.2, 6.3 Hz, 1 H), 4.17 (dd, *J* = 11.2, 5.8 Hz, 1 H), 3.96–3.76 (m, 4 H), 3.16 (d, *J* = 2.0 Hz, 1 H), 2.63 (td, *J* = 12.4, 1.1 Hz, 1 H), 2.60 (t, *J* = 6.2 Hz, 1 H), 2.35 (td, *J* = 14.6, 4.1 Hz, 1 H), 2.22–1.74 (m, 8 H), 1.42–1.23 (m, 3 H), 0.84 (s, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 210.4, 194.8, 151.7, 125.2, 117.3, 65.6, 65.4, 64.8, 64.7, 63.2, 59.9, 49.6, 49.3, 49.1, 46.2, 37.8, 34.2, 30.1, 29.7, 22.1, 15.1.



Diepoxide 51: Enone **50** from the aforementioned reaction (assumed to be 5.55 mmol) was dissolved in MeOH (56 mL) and cooled to 0 ºC. 10% NaOH aqueous solution (2.0 mL, 1.0 equiv) was added, followed by 35% H_2O_2 (2.84 mL, 6 equiv, added in 3 portions in 25 min intervals). The reaction was diluted with EtOAc (75 mL) and quenched with sat. aq. $Na_2S_2O_3$ (75 mL) at 0 ºC. After warming to room temperature, H_2O was added to dissolve the white precipitate that was formed upon quenching. The aqueous layer was extracted with EtOAc (2 x 125 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. After a short silica plug (washing with EtOAc), an off-white foam (1.08 g, 50% over 3 steps) was obtained, which was pure enough to be used for the next step.

Physical state: foam.

$\boldsymbol{R_f}$ = 0.28 (silica gel, 3:2 EtOAc:hexanes).

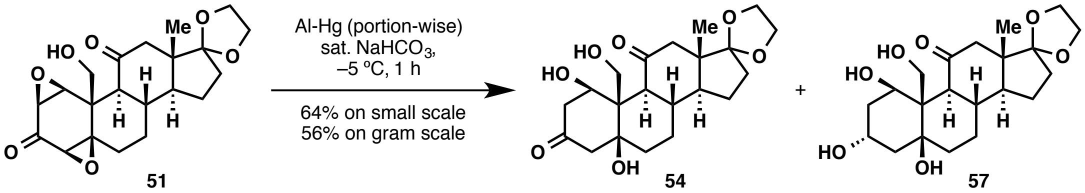
HRMS (*m*/*z*): calcd for $C_{21}H_{26}O_7$, $[M+H]^+$, 391.1751; found, 391.1769.

$[\alpha]_D$ = +62.9° (*c* = 1.0, CH_2Cl_2).

IR (film) ν_{max}: 3461, 2946, 2879, 1700, 1165, 1101, 1056, 915, 735.

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.56 (dd, *J* = 11.7, 3.4 Hz, 1 H), 4.30 (dd, *J* = 11.7, 9.2 Hz, 1 H), 4.07 (d, *J* = 4.0 Hz, 1 H), 3.99–3.77 (m, 4 H), 3.29 (dd, *J* = 4.0, 2.5 Hz, 1 H), 3.16 (dd, *J* = 9.2, 3.4 Hz, 1 H), 3.09 (d, *J* = 2.5 Hz, 1 H), 2.76 (d, *J* = 11.9 Hz, 1H), 2.24 (d, *J* = 1.1 Hz, 1 H), 2.24–2.16 (m, 1 H), 2.18 (d, *J* = 11.9 Hz, 1 H), 2.11–1.90 (m, 4 H), 1.86 – 1.74 (m, 1 H), 1.45–1.21 (m, 2 H), 1.07 (dt, *J* = 13.9, 3.3 Hz, 1 H), 0.86 (s, 3 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 211.7, 200.5, 117.2, 72.7, 65.6, 64.7, 63.2, 63.2, 61.2, 59.2, 54.8, 50.1, 49.8, 49.4, 42.1, 37.6, 34.3, 31.7, 29.9, 22.0, 15.0.



Triol 54: Diepoxide **51** (1.18 g, 2.56 mmol) was suspended in saturated aqueous $NaHCO_3$ (350 mL) and cooled to –5 ºC. Then, aluminum foil (11.0 g) was cut into small strips and immersed in 2% aqueous $HgCl_2$ solution (540 mL) for 30 s. The aluminum strips were collected by vacuum filtration and sequentially washed with EtOH (150 mL) and Et_2O (150 mL). The strips were then added piecewise to the heterogeneous reaction mixture over 1 h, followed by addition of THF (10 mL). After another 10 min period, the mixture was diluted with EtOAc and filtered through Celite®, which was washed with EtOAc (200 mL). The aqueous layer was washed with EtOAc (2 x 75 mL) and the combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4. After filtration and concentration *in vacuo,* the crude product was purified by silica gel chromatography (1:1 to 1:0 EtOAc:hexanes) to give **54** (664 mg, 56%) as a white solid, 95 mg of recovered **51**, and 137 mg (13%) of tetraol **57**.

Analytical data for compound **54**:

Physical state: white solid (decomp. 120–130 °C).

$\boldsymbol{R_f}$ = 0.20 (silica gel, 4:1 EtOAc:hexanes).

HRMS (*m/z*): calcd for $C_{21}H_{30}O_7$, $[M+H]^+$, 395.2064; found, 395.2065.

$[\alpha]_D$ = +8.2° (c = 0.8, CH_2Cl_2).

IR (film) ν_{max}: 3409, 2943, 2875, 1705, 1424, 1166, 1038, 908.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.09 (s, 1 H), 4.87 (q, *J* = 3.9 Hz, 1 H), 4.58 (dd, *J* = 11.7, 2.9 Hz, 1 H), 4.41 (td, *J* = 12.1, 1.3 Hz, 1 H), 4.32 (dd, *J* = 3.9, 2.0 Hz, 1 H), 4.13 (dd, *J* = 12.5, 2.9 Hz, 1 H), 4.01–3.80 (m, 4 H), 2.92 (d, *J* = 15.2 Hz, 1 H), 2.81 (dt, *J* = 11.7, 1.0 Hz, 1 H), 2.65 (ddd, *J* = 15.4, 3.8, 2.4 Hz, 1 H), 2.58 (d, *J* = 11.0 Hz, 1 H), 2.49 (ddd, *J* = 15.4, 4.3, 2.0 Hz, 1 H), 2.31 (dd, *J* = 15.2, 2.4 Hz, 1 H), 2.19 (d, *J* = 11.7 Hz, 1 H), 2.16–2.09 (m, 1 H), 2.07 (dt, *J* = 11.6, 3.3 Hz, 1 H), 1.98 (ddd, *J* = 14.5, 9.6, 6.3 Hz, 1 H), 1.91–1.78 (m, 3 H), 1.57 (td, *J* = 14.0, 4.0 Hz, 1 H), 1.46 (ddd, *J* = 15.2, 5.1, 3.2 Hz, 1 H), 1.39 (dd, *J* = 12.2, 6.5 Hz, 1 H), 1.35–1.20 (m, 1 H), 0.87 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 214.9, 207.8, 117.2, 78.8, 73.8, 65.6, 64.7, 61.7, 58.1, 50.7, 50.0, 49.9, 49.8, 45.7, 44.4, 38.1, 34.4, 34.0, 27.6, 22.0, 15.1.

Analytical data for tetraol **57**:

Physical state: white solid.

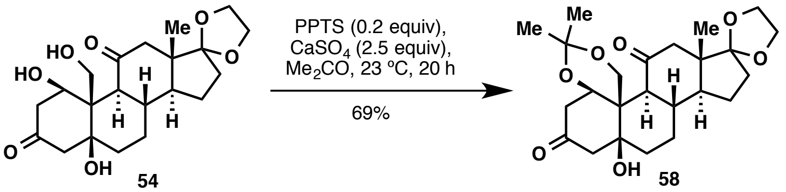
$\boldsymbol{R_f}$ = 0.13 (silica gel, EtOAc).

HRMS (*m/z*): calcd for $C_{21}H_{32}O_7$, $[M+H]^+$, 397.2226; found, 397.2232.

IR (film) ν_{max}: 3417, 2932, 2875, 1690, 1458, 1386, 1260, 1168, 1100, 1089.

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.92 (s, 1 H), 4.78 (dd, *J* = 12.1, 2.5 Hz, 1 H), 4.59 (t, *J* = 3.3 Hz, 1 H), 4.44–4.39 (m, 1 H), 4.35 (t, *J* = 12.3 Hz, 1 H), 4.23 (dd, *J* = 3.7, 1.9 Hz, 1 H), 4.01–3.78 (m, 5 H), 2.74 (d, *J* = 11.4 Hz, 1 H), 2.61 (d, *J* = 11.0 Hz, 1 H), 2.19–2.15 (m, 1 H), 2.13–2.08 (m, 1 H), 2.10 (d, *J* = 11.4 Hz, 1 H), 2.08–2.01 (m, 1H), 1.96 (td, *J* = 9.1, 8.5, 4.8 Hz, 1 H), 1.91 (t, *J* = 11.8 Hz, 1 H), 1.81–1.66 (m, 4 H), 1.47–1.38 (m, 3 H), 1.32 (ddt, *J* = 15.5, 10.6, 4.6 Hz, 2 H), 0.82 (s, 3 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 216.0, 117.3, 75.8, 71.6, 65.6, 64.8, 63.5, 61.4, 57.3, 50.9, 50.0, 49.9, 45.0, 42.2, 38.4, 36.3, 34.5, 34.1, 27.0, 21.9, 15.0.



Acetonide 58: Triol **54** (1.06 g, 2.69 mmol) was dissolved in acetone (106 mL) and stirred at room temperature with PPTS (135 mg, 0.54 mmol, 0.2 equiv) and anhydrous CaSO$_4$ (916 mg, 6.73 mmol, 2.5 equiv). After 24 h, the reaction was neutralized with K$_2$CO$_3$, filtered through a pad of Celite® and concentrated *in vacuo*. Silica gel chromatography purification (1:3 to 1:1 EtOAc:hexanes) afforded pure **58** (807 mg, 69%) as a white solid.

Physical state: white solid (m.p. 175–176 °C).

R$_f$ = 0.50 (silica gel, 4:1 EtOAc:hexanes).

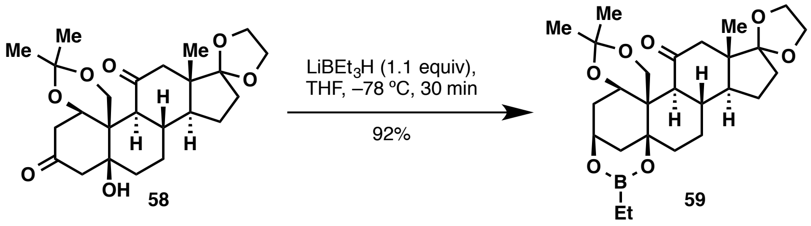
HRMS (*m/z*): calcd for $C_{24}H_{34}O_7$, [M+Na]$^+$, 457.2197; found, 457.2188.

$[\alpha]_D$ = +9.2° (*c* = 0.5, CH$_2$Cl$_2$).

IR (film) ν_{max}: 3490, 2940, 2875, 1702, 1384, 1202, 1168, 1097, 1052.

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.42 (dd, *J* = 4.8, 2.6 Hz, 1 H), 4.64 (d, *J* = 12.1 Hz, 1 H), 4.59 (s, 1 H), 4.17 (d, *J* = 12.0 Hz, 1 H), 3.95–3.74 (m, 4 H), 2.84 (d, *J* = 14.5 Hz, 1 H), 2.66 (d, *J* = 12.1 Hz, 1 H), 2.46 (dd, *J* = 15.4, 4.7 Hz, 1 H), 2.40–2.30 (m, 2 H), 2.22 (dd, *J* = 14.5, 2.6 Hz, 1 H), 2.10 (d, *J* = 12.0 Hz, 1 H), 2.04–1.75 (m, 5 H), 1.69 (s, 3 H), 1.65–1.50 (m, 2 H), 1.38–1.14 (m, 2 H), 1.32 (s, 3 H), 0.78 (s, 3 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 210.3, 207.3, 117.3, 99.7, 79.8, 71.3, 65.5, 64.6, 60.7, 54.4, 50.4, 49.9, 49.7, 49.6, 43.3, 39.4, 36.5, 35.5, 34.1, 28.8, 28.6, 22.2, 20.2, 14.9.



Boronate 59: Acetonide **58** (1.02 g, 2.35 mmol) was dissolved in THF (47 mL) under Ar. After cooling to –78 ºC, 1 M solution of $LiBEt_3H$ in THF (2.6 mL, 1.1 equiv) was added dropwise. After 30 min, acetone (5 mL) was added at –78 ºC to quench any remaining active hydride species. EtOAc (30 mL) and sat. aq. NH_4Cl (50 mL) was added and the mixture was warmed to room temperature, after which 1 M NaOH solution (25 mL) was added to dissolve the white precipitate that was formed. The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organic layers were washed with brine (75 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting amorphous solid was passed through a short pad of silica gel, washed with 1:1 EtOAc:hexanes and concentrated to afford **59** (1.02 g, 92%) as an amorphous solid that was sufficiently pure for the next step.

Physical state: amorphous solid.

$\boldsymbol{R_f}$ = 0.54 (silica gel, 3:2 EtOAc:hexanes).

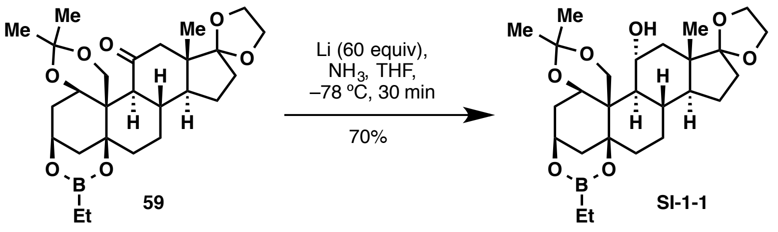
HRMS (*m*/*z*): calcd for $C_{26}H_{39}BO_7$, $[M+H]^+$, 475.2861; found, 475.2872.

$[\alpha]_D$ = +24.2° (c = 0.5, CH_2Cl_2).

IR (film) ν_{max}: 2938, 2878, 1707, 1332, 1201, 1165, 1099, 909.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 (d, J = 2.8 Hz, 1 H), 4.26 (d, J = 11.9 Hz, 1 H), 4.20 (s, 1H), 3.95 (d, J = 12.0 Hz, 1 H), 3.95–3.74 (m, 4 H), 2.59 (d, J = 11.8 Hz, 1 H), 2.20 (d, J = 11.5 Hz, 1 H), 2.19 (dd, J = 14.1, 2.2 Hz, 1 H), 2.11 (dq, J = 16.4, 2.6 Hz, 1 H), 2.07 (d, J = 11.9 Hz, 1 H), 2.02–1.58 (m, 8 H), 1.55–1.46 (m, 1 H), 1.50 (s, 3H), 1.40–1.15 (m, 3 H), 1.32 (s, 3 H), 0.87 (t, J = 7.7 Hz, 3 H), 0.80 (s, 3 H), 0.68 (q, J = 7.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 209.4, 117.5, 99.7, 72.5, 66.2, 65.5, 65.0, 64.7, 60.2, 55.4, 50.4, 50.0, 49.7, 43.6, 36.5, 35.4, 35.3, 34.3, 33.5, 27.1, 25.7, 23.1, 22.2, 15.1, 7.9.



Alcohol SI-1-1: In a flask equipped with a dry ice condenser containing ammonia (ca. 200 mL) at –78 ºC was added lithium wire (1224 mg, 60.0 equiv). After 15 min, acetonide **59** (1400 mg, 2.95 mmol) in THF (98 mL) was introduced to the blue ammonia solution at –78 ºC. The reaction was allowed to stir for 30 min and then quenched with dropwise addition of 10:1 THF:*t*BuOH (30 mL), followed by sat. aq. NH_4Cl (75 mL). After warming to room temperature, the aqueous layer was extracted with EtOAc (2 x 150 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting colorless oil was purified by column chromatography (3:1 to 3:2 EtOAc:hexanes) to give the corresponding alcohol **SI-1-1** (980 mg, 70%) as an amorphous solid.

Physical state: amorphous solid.

R_f = 0.44 (silica gel, 3:2 EtOAc:hexanes).

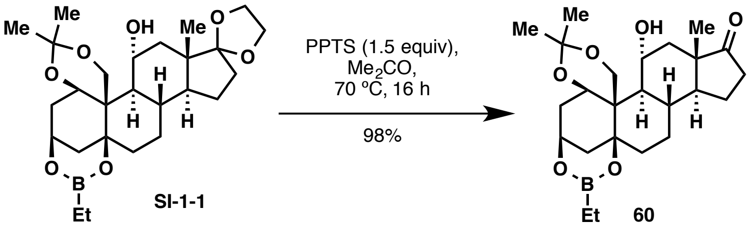
HRMS (*m/z*): calcd for $C_{26}H_{41}BO_7$, $[M+H]^+$, 477.3018; found, 477.3014.

$[\alpha]_D = -5.0°$ (c = 0.5, CH_2Cl_2).

IR (film) ν_{max}: 3466, 2934, 2876, 1379, 1333, 1226, 1203, 1092.

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.23 (dd, *J* = 5.2, 2.0 Hz, 1 H), 4.35 (d, *J* = 12.0 Hz, 1 H), 4.26–4.19 (m, 1 H), 4.15 (ddd, *J* = 10.8, 8.7, 5.0 Hz, 1 H), 3.96 – 3.79 (m, 4H), 3.72 (d, *J* = 12.0 Hz, 1H), 2.17–2.09 (m, 2 H), 1.98 (ddd, *J* = 14.6, 11.6, 3.0 Hz, 1 H), 1.91–1.83 (m, 1 H), 1.83–1.75 (m, 1 H), 1.72 (dd, *J* = 11.9, 4.9 Hz, 1 H), 1.66–1.57 (m, 2 H), 1.50 (ddt, *J* = 15.1, 10.3, 3.8 Hz, 4 H), 1.39–1.33 (m, 1 H), 1.31 (s, 3 H), 1.28 (s, 3 H), 1.26–1.18 (m, 3 H), 1.08–0.96 (m, 1 H), 0.89 (s, 3 H), 0.88 (t, *J* = 7.7 Hz, 3 H), 0.66 (q, *J* = 7.6 Hz, 2 H).

^{13}C NMR(CDCl$_3$, 101 MHz): δ 118.6, 101.5, 72.4, 69.9, 67.1, 65.4, 65.2, 64.7, 60.5, 51.2, 49.3, 49.0, 46.4, 42.0, 37.1, 35.2, 34.9, 34.3, 33.2, 25.7, 24.2, 23.2, 22.6, 15.8, 7.9.



Alcohol 60: To the above alcohol (1020 mg, 2.14 mmol) in acetone (42 mL) at room temperature was added PPTS (807 mg, 3.21 mmol, 1.5 equiv). The solution was then heated to 70 ºC and stirred for 16 h. Upon completion of the reaction, the solution was concentrated *in vacuo* and redissolved in EtOAc before being filtered through a short pad of silica gel, washing with EtOAc. Concentration *in vacuo* afforded **60** (907 mg, 98%) as an amorphous solid. Note that the R_f of the product is the same as that of

the starting material in an EtOAc:hexanes solvent system, thus the reaction was monitored by NMR spectra of its aliquot.

Physical state: amorphous solid.

$\boldsymbol{R_f}$ = 0.44 (silica gel, 3:2 EtOAc:hexanes).

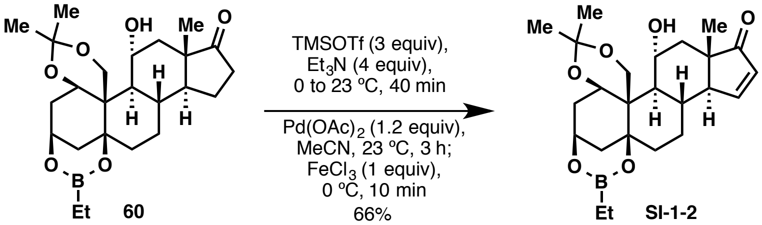
HRMS (*m/z*): calcd for $C_{24}H_{37}BO_6$, $[M+H]^+$, 433.2756; found, 433.2759.

$[\alpha]_D$ = +51.5° (c = 0.5, CH_2Cl_2).

IR (film) ν_{max}: 3456, 2933, 2870, 1737, 1403, 1378, 1333, 1223, 1206, 1092.

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.27 (dd, *J* = 5.1, 2.0 Hz, 1 H), 4.37 (dd, *J* = 12.0, 1.3 Hz, 1 H), 4.29–4.17 (m, 2 H), 3.70 (d, *J* = 12.1 Hz, 1 H), 2.46 (dd, *J* = 19.5, 8.4 Hz, 1 H), 2.22 –2.05 (m, 5 H), 1.97–1.84 (m, 2 H), 1.67–1.58 (m, 1 H), 1.57–1.48 (m, 3 H), 1.46–1.36 (m, 3 H), 1.31 (s, 3 H), 1.27 (s, 3 H), 1.27–1.22 (m, 1 H), 1.17–1.01 (m, 1 H), 0.90 (s, 3 H), 0.87 (t, *J* = 7.7 Hz, 3 H), 0.67 (q, *J* = 7.7 Hz, 2 H).

^{13}C NMR(CDCl$_3$, 101 MHz): δ 218.8, 101.5, 72.4, 68.9, 67.0, 65.3, 60.7, 51.5, 49.9, 49.3, 48.1, 42.6, 37.1, 35.9, 35.3, 34.4, 33.2, 25.4, 24.3, 23.2, 21.9, 15.0, 7.9.



Enone SI-1-2: Ketone **60** (1140 mg, 2.634 mmol) was dissolved in CH_2Cl_2 (54 mL). After cooling to 0 °C, Et_3N (1.47 mL, 10.56 mmol, 4.0 equiv) was added to the solution, followed by TMSOTf (1.44 mL, 7.92 mmol, 3.0 equiv) dropwise. After 20 min, the solution was warmed to room temperature, stirred for another 20 min period before being poured into ice-cold sat. aq. $NaHCO_3$ solution. The aqueous layer was then extracted with hexanes (3 x 75 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was used for the next step without further purification.

The aforementioned oil was dissolved in MeCN (54 mL), followed by the addition of $Pd(OAc)_2$ (711 mg, 3.18 mmol, 1.2 equiv). After 3 h of stirring, the dark brown solution was cooled to 0 °C and $FeCl_3$ (750 mg, 2.778 mmol, 1.0 equiv) was added in one portion. After 10 min, the mixture was neutralized with the addition of K_2CO_3 (1092 mg, 7.92 mmol, 3.0 equiv). Following filtration through a short pad of silica gel, the crude mixture was concentrated and then purified by column chromatography to provide pure **SI-1-2** (750 mg, 66%) as a white solid.

Physical state: white soild (m.p. 210–211 ºC).

***R**$_f$* = 0.44 (silica gel, 3:2 EtOAc:hexanes).

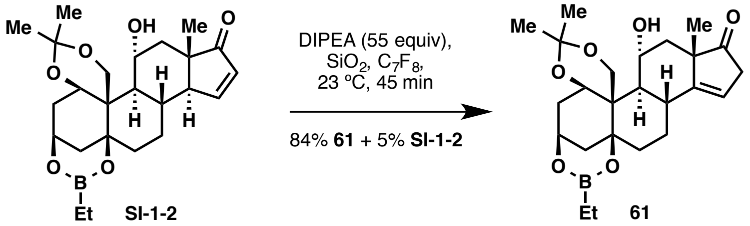
HRMS (*m/z*): calcd for $C_{24}H_{35}BO_6$, $[M+H]^+$, 431.2599; found, 431.2595.

$[\alpha]_D$ = –22.7° (*c* = 0.5, CH_2Cl_2).

IR (film) ν_{max}: 3448, 2932, 2873, 1708, 2459, 1403, 1378, 1334, 1287, 1226, 1205.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 5.9, 1.7 Hz, 1 H), 6.07 (dd, *J* = 5.9, 3.1 Hz, 1 H), 5.19 (dd, *J* = 4.8, 2.1 Hz, 1 H), 4.48 (td, *J* = 9.5, 6.2 Hz, 1 H), 4.39 (dd, *J* = 12.1, 1.4 Hz, 1 H), 4.28–4.16 (m, 1 H), 3.73 (d, *J* = 12.1 Hz, 1 H), 2.40 (dt, *J* = 11.7, 2.2 Hz, 1 H), 2.34 (dd, *J* = 12.3, 6.2 Hz, 1 H), 2.27 (dd, *J* = 13.8, 2.1 Hz, 1 H), 2.16–2.09 (m, 1 H), 1.95 (ddd, *J* = 15.3, 5.0, 2.8 Hz, 1 H), 1.84 (dq, *J* = 12.9, 3.6 Hz, 1 H), 1.73 (ddd, *J* = 22.5, 11.6, 3.3 Hz, 1 H), 1.62 (td, *J* = 13.7, 4.0 Hz, 1 H), 1.58–1.45 (m, 3 H), 1.40–1.33 (m, 1 H), 1.31 (s, 3 H), 1.29 (s, 3 H), 1.25–1.16 (m, 1 H), 1.08 (s, 3 H), 0.89 (t, *J* = 7.8 Hz, 3 H), 0.68 (q, *J* = 7.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 211.3, 157.4, 132.6, 101.3, 72.5, 67.7, 67.1, 65.5, 61.4, 54.9, 53.4, 50.6, 49.4, 40.9, 37.2, 35.4, 33.1, 32.9, 25.7, 24.3, 23.2, 21.8, 7.9.



Enone 61: SiO_2 (3500 mg) was added to **SI-1-2** (500 mg, 1.16 mmol), followed by C_7F_8 (30 mL) and DIPEA (11.4 mL, 63.8 mmol, 55 equiv). The mixture was then stirred at room temperature and monitored by TLC until satisfactory conversion was observed (typically 45 min to 1 h). The mixture was filtered through a Celite® pad and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography to provide **61** (420 mg, 84%) as a white foam and recovered **SI-1-2** (26 mg, 5%).

Physical state: white foam.

***R**$_f$* = 0.62 (silica gel, 3:2 EtOAc:hexanes).

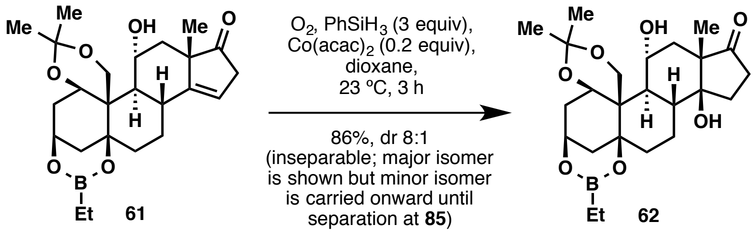
HRMS (*m/z*): calcd for $C_{24}H_{35}BO_6$, $[M+H]^+$, 431.2599; found, 431.2596.

$[\alpha]_D$ = +63.4° (*c* = 1.0, CH_2Cl_2).

IR (film) ν_{max}: 3455, 2933, 2875, 1743, 1403, 1377, 1333, 1286, 1225, 1203, 1051.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.56 (d, *J* = 2.1 Hz, 1 H), 5.09 (dd, *J* = 5.3, 1.9 Hz, 1 H), 4.41 (dd, *J* = 12.1, 1.3 Hz, 1 H), 4.20 (tq, *J* = 8.8, 3.4 Hz, 2 H), 3.82 (d, *J* = 12.1 Hz, 1 H), 3.63 (d, *J* = 4.1 Hz, 1 H), 3.03 (ddd, J = 23.0, 3.7, 1.8 Hz, 1 H), 2.82 (dt, J = 22.9, 2.2 Hz, 1 H), 2.10 (td, J = 14.4, 13.6, 2.2 Hz, 2 H), 1.99 (dd, J = 12.7, 3.7 Hz, 2 H), 1.83 (ddd, J = 15.4, 5.3, 2.7 Hz, 1 H), 1.76–1.65 (m, 1 H), 1.6–1.49 (m, 3 H), 1.44 (dd, J = 9.3, 2.9 Hz, 1 H), 1.36 (t, J = 12.0 Hz, 1 H), 1.33 (s, 3 H), 1.28 (s, 3 H), 1.23–1.17 (m, 1 H), 1.17 (s, 3 H), 0.87 (t, J = 7.7 Hz, 3 H), 0.67 (q, J = 7.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 151.1, 114.9, 102.1, 71.8, 70.5, 67.3, 64.8, 59.7, 50.8, 50.7, 49.0, 41.9, 41.5, 36.2, 35.1, 34.6, 33.3, 24.0, 23.3, 22.9, 21.8, 20.6, 7.8.



'Protected ouabageninone' 62: A solution of **61** (600 mg, 1.39 mmol) in dioxane (30 mL) was saturated with O_2 by bubbling O_2 through the stirred solution for 15 min. To this solution was added Co(acac)$_2$ (72 mg, 0.278 mmol, 0.2 equiv). A solution of $PhSiH_3$ (0.516 mL, 4.18 mmol, 3.0 equiv) in dioxane (3 mL) was added over 60 min via syringe pump. The stirring was continued under an O_2 atmosphere (no bubbling) at ambient temperature for approximately 3 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (40 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed sequentially with sat. aq. $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The green oil obtained was purified by silica gel chromatography (2:3 to 3:2 EtOAc:hexanes) to provide **62** (538 mg, 86%, isolated as an inseparable mixture of diastereomers in a ratio of 8:1 in favor of the desired one) as a white solid.

Physical state: white solid.

$\boldsymbol{R_f}$ = 0.36 (silica gel, 3:2 EtOAc:hexanes).

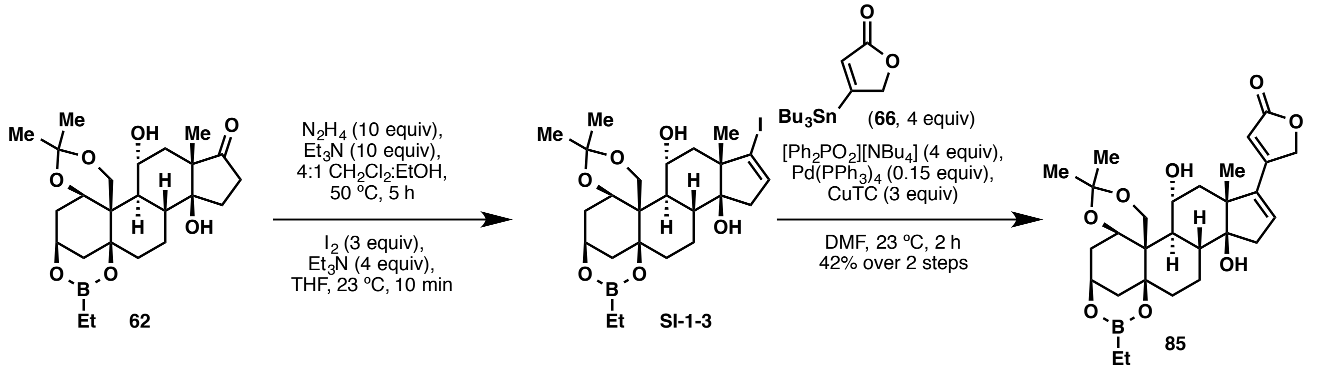
HRMS (*m/z*): calcd for $C_{24}H_{37}BO_7$, $[M+H]^+$, 449.2705; found, 449.2710.

$[\alpha]_D$ = +19.4° (c = 1.0, CH_2Cl_2).

IR (film) ν_{max}: 3418, 2935, 2875, 1730, 1644, 1402, 1378, 1334, 1281, 1223, 1205, 1056.

^{1}H NMR (400 MHz, $CDCl_3$): (major diastereomer) δ 5.12 (dd, J = 5.5, 2.0 Hz, 1 H), 4.40 (d, J = 12.1 Hz, 1 H), 4.33–4.21 (m, 1 H), 4.06 (tt, J = 8.2, 4.1 Hz, 1 H), 3.76 (d, J = 12.2 Hz, 1 H), 3.22 (d, J = 4.4 Hz, 1 H), 2.52–2.40 (m, 2 H), 2.23–2.14 (m, 2 H), 2.09 (dd, J = 13.8, 2.0 Hz, 1 H), 1.94–1.84 (m, 3 H), 1.65 –1.44 (m, 6 H), 1.34 (s, 3 H), 1.31–1.23 (m, 1 H), 1.29 (s, 3 H), 1.15 (s, 3 H), 0.90 (t, J = 7.7 Hz, 3 H), 0.70 (q, J = 7.7 Hz, 2 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 219.2, 102.0, 81.6, 71.6, 69.2, 67.2, 64.7, 59.7, 53.8, 48.8, 45.9, 41.5, 41.1, 36.6, 35.1, 33.4, 33.1, 27.7, 24.0, 23.2, 20.5, 14.5, 7.9.



Dienoate 85: To a solution of **62** (30 mg, 66.7 *μ*mol) in 4:1 mixture of CH$_2$Cl$_2$/EtOH (1.2 mL) was added anhydrous N$_2$H$_4$ (21 *μ*L, 667 *μ*mol, 10.0 equiv) and Et$_3$N (93 *μ*L, 667 *μ*mol, 10.0 equiv). The mixture was heated at 50 °C for 5 h, after which the reaction was allowed to cool and concentrated *in vacuo*. The residue thus obtained was dissolved in degassed THF (1.4 mL), upon which Et$_3$N (38 *μ*L, 268 *μ*mol, 4 equiv) was added. A stock solution of I$_2$ (52 mg, 202 *μ*mol, 3.0 equiv) in THF (0.4 mL) was prepared and added dropwise to the reaction mixture. After the solution stayed brown for more than 30 s, addition was halted and stirring was continued for 10 min. The reaction was then diluted with EtOAc (5 mL) and washed with sat. aq. Na$_2$S$_2$O$_3$ (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic portions were washed with sat. aq. NaCl (10 mL), dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The residue obtained was passed through a short pad of silica gel, and washed with 1:1 hexanes:EtOAc. Concentration *in vacuo* afforded vinyl iodide **SI-1-3**, which was used for the next step without further purification.

The above iodide and stannane **66** (100 mg, 268 *μ*mol, 4.0 equiv) were dissolved in DMF (1.1 mL) and the resulting solution was degassed by bubbling argon for 15 min. To this solution was sequentially added [Ph$_2$PO$_2$][NBu$_4$] (123 mg, 268 μmol, 4.0 equiv), Pd(PPh$_3$)$_4$ (11 mg, 10 μmol, 0.15 equiv) and CuTC (38 mg, 200 μmol, 3.0 equiv). The reaction mixture was stirred for 2 h and then quenched with water (2.5 mL). The suspension was passed through a pad of Celite®, which was washed with EtOAc (10 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic layers were successively washed with sat. aq. NaHCO$_3$ (10 mL), H$_2$O (2 x 5 mL) and sat. aq. NaCl (10 mL), dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (1:1 to 4:1 EtOAc:hexanes) afforded dienoate **85** (15 mg, 42% over 2 steps) as a white solid.

Physical state: white solid (m.p. 234–235 ºC).

R_f = 0.37 (silica gel, EtOAc).

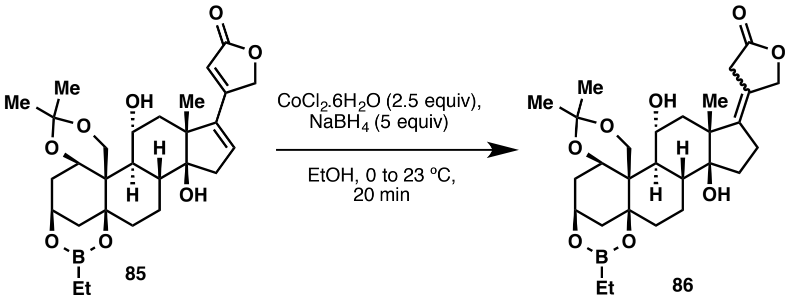
HRMS (*m*/*z*): calcd for $C_{28}H_{39}BO_8$, $[M+H]^+$, 515.2811; found, 515.2828.

$[\alpha]_D$ = +20.0° (c = 0.4, CH_2Cl_2).

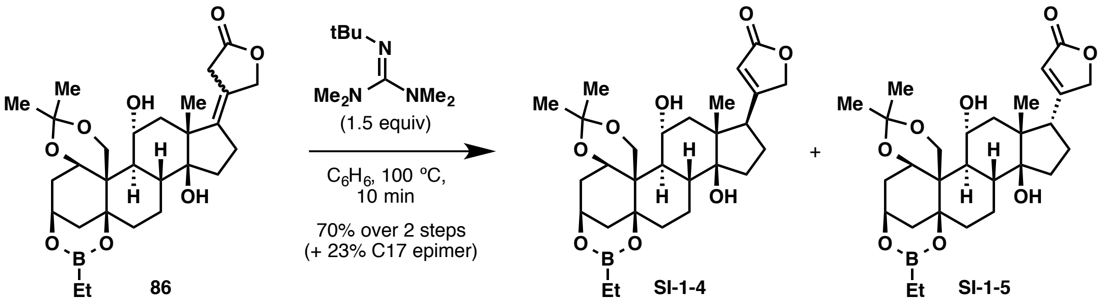
IR (film) ν_{max}: 3451, 2956, 2929, 2875, 2247, 1783, 1739, 1622, 1460, 1404, 1378, 1335, 1287, 1224.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.11 (s, 1 H), 6.00 (s, 1 H), 5.01 (m, 1 H), 4.98 (dd, *J* = 16.4, 1.8 Hz, 1 H), 4.92 (dd, *J* = 16.4, 1.8 Hz, 1 H), 4.43 (d, *J* = 12.1 Hz, 1 H), 4.27 (t, *J* = 2.9 Hz, 1 H), 4.02 (ddd, *J* = 11.8, 9.0, 3.2 Hz, 1 H), 3.80 (d, *J* = 12.2 Hz, 1 H), 2.73 (d, *J* = 18.7 Hz, 1 H), 2.43 (dd, *J* = 18.7, 3.4 Hz, 1 H), 2.18 (td, *J* = 13.7, 2.9 Hz, 2 H), 2.06 (dd, *J* = 13.7, 1.8 Hz, 1 H), 2.01 (dt, *J* = 12.0, 3.9 Hz, 1 H), 1.88 (ddd, *J* = 15.3, 5.4, 2.8 Hz, 1 H), 1.61–1.49 (m, 4 H) 1.47–1.40 (m, 2 H), 1.37 (s, 3 H), 1.36 (s, 3 H) 1.31 (s, 3 H), 1.19 (qd, *J* = 13.6, 3.7 Hz, 1 H), 0.87 (t, *J* = 7.7 Hz, 3 H), 0.67 (q, *J* = 7.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 174.1, 157.8, 143.3, 131.8, 113.3, 102.2, 84.7, 71.7, 71.5, 68.9, 67.4, 64.6, 59.8, 52.7, 48.5, 47.4, 46.1, 41.1, 40.4, 36.4, 35.1, 33.5, 29.9, 23.9, 23.2, 21.8, 18.5, 7.9.



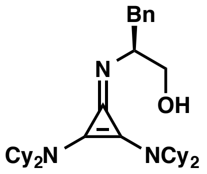
Enoate 86: To a solution of dienoate **85** (10 mg, 19.4 μmol) in EtOH (200 μL) was added $CoCl_2 \cdot 6H_2O$ (11.5 mg, 48.5 μmol, 2.5 equiv). The blue solution was cooled to 0 ºC and solid $NaBH_4$ (3.7 mg, 97 μmol, 5.0 equiv) was added. After evolution of gas had ceased and the mixture turned black (typically within 5 min), the mixture was warmed to rt. After further stirring for 20 min, the mixture was filtered through a pad of Celite®, which was washed with EtOAc (10 mL). Concentration *in vacuo* afforded enoate **86** (10 mg, 100%) as a mixture of olefin isomers, which was used for the next step without further purification.



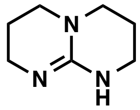
Enoate SI-1-4: A solution of enoate **86** (10 mg, 19.4 μmol) in C_6H_6 (200 μL) was pre-heated to 100 ºC before a stock solution of Barton's base (see details of base screening in **Table S1** below) in C_6H_6 (0.6 M, 50 μmol, ca. 1.5 equiv) was added. After 10 min, the solution was cooled to room temperature and then concentrated *in vacuo*. NMR analysis of the crude reaction mixture revealed a 3:1 β:α butenolide ratio at C17. These diastereomers can be separated by preparative TLC (2:1 MTBE:Et_2O) to afford enoate **SI-1-4** (7.0 mg, 70%) as a white solid and the C17 epimer **SI-1-5** (2.3 mg, 23%).

Table S1. Optimization of conditions for the isomerization reaction

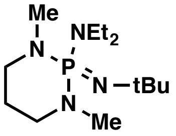
Conditions	**SI-1-4 : SI-1-5**	**Conditions**	**SI-1-4 : SI-1-5**
$RhCl_3$	No reaction	TBD, C_6D_6	1:3.8
AcOH, $CDCl_3$	No reaction	TMG, C_6D_6	0:1
TBAF, THF	Decomposition	Quinine, C_6D_6	No reaction
DBU, $CDCl_3$	No reaction	**SI-1-6**	0:1
DBU, C_6D_6	1:4	BTMG, C_6D_6	1:1.3
Proton sponge, C_6D_6	No reaction	BTMG, $PhCF_3$	1:1.7
Verkade's base, C_6D_6	Decomposition	BTMG, MeCN	0:1
BEMP, C_6D_6	1:11	BTMG, CD_2Cl_2	1:2.5
Schwesinger P_1, C_6D_6	1:4.2	BTMG, C_6H_6, 100 °C	3:1



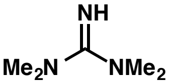
SI-1-6



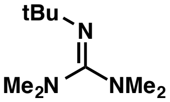
TBD



BEMP



TMG



BTMG

SI-1-4 was found to match with a ouabagenin derivative (see SI-Spectra file) that was prepared from commercial ouabain using the following procedure: Ouabain octahydrate was converted to ouabagenin-

11,19-acetonide following the procedure described by Mannich.[1] A suspension of this acetonide (15 mg, 31.3 μmol) in THF (1 mL) was cooled to –78 ºC and then treated with 1 M solution of $LiBEt_3H$ in THF (38 μL, 38 μmol, ca. 1.2 equiv). After 30 min, the reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL), warmed to room temperature and stirred for 1 h. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel chromatography (3:1 EtOAc:hexanes to EtOAc) afforded **SI-1-4** (8 mg, 49%) as a white solid.

Analytical data for **SI-1-4**:

Physical state: white solid (m.p. 235 ºC).

R_f = 0.36 (silica gel, EtOAc).

HRMS (*m/z*): calcd for $C_{28}H_{41}BO_8$, $[M+H]^+$, 517.2967; found, 517.2987.

$[\alpha]_D$ = +22.4° (c = 0.4, CH_2Cl_2).

IR (film) ν_{max}: 3455, 2956, 2932, 2875, 1737, 1623, 1403, 1378, 1341, 1289, 1225, 1205.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.91 (s, 1 H), 5.04 (dd, J = 5.3, 1.8 Hz, 1 H), 4.93 (dd, J = 18.0, 1.7 Hz, 1 H), 4.80 (dd, J = 17.9, 1.7 Hz, 1 H), 4.38 (d, J = 12.1 Hz, 1 H), 4.27 (s, 1 H), 4.11 (td, J = 7.9, 4.0 Hz, 1 H), 3.74 (d, J = 12.1 Hz, 1 H), 3.10 (d, J = 4.2 Hz, 1 H), 2.89 (dd, J = 9.0, 6.2 Hz, 1 H), 2.22–2.15 (m, 2 H) 2.11 (dt, J = 13.7, 9.7 Hz, 1 H), 2.06 (dd, J = 13.7, 1.9 Hz, 1 H), 1.95–1.82 (m, 3 H), 1.80–1.70 (m, 2 H), 1.61 (dt, J = 13.9, 2.8 Hz, 1 H), 1.55 (dt, J = 13.9, 2.8 Hz, 1 H), 1.53–1.39 (m, 3 H), 1.34 (s, 3 H), 1.29 (s, 3 H), 1.19 (m, 1 H), 0.97 (s, 3 H), 0.90 (t, J = 7.7 Hz, 3 H), 0.69 (q, J = 7.7 Hz, 2 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 174.3, 173.3, 118.2, 101.9, 84.7, 73.6, 71.7, 69.3, 67.2, 64.8, 59.9, 50.2, 49.7, 48.9, 48.7, 45.8, 41.2, 36.6, 35.0, 33.8, 33.3, 29.8, 27.2, 24.1, 23.2, 22.0, 17.8, 7.9.

Analytical data for C17-epimer **SI-1-5**:

R_f = 0.36 (silica gel, EtOAc).

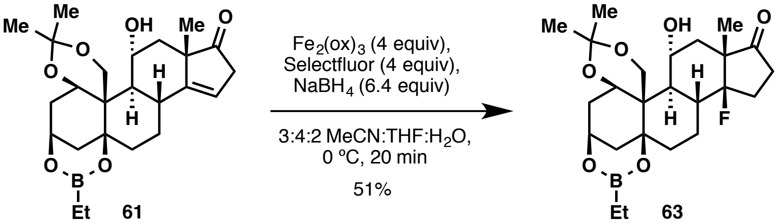
HRMS (*m/z*): calcd for $C_{28}H_{41}BO_8$, $[M+H]^+$, 517.2967; found, 517.2987.

IR (film) ν_{max}: 3400, 2956, 2932, 2875, 1746, 1624, 1403, 1378, 1333, 1226, 1205.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.91 (d, J = 1.9 Hz, 1 H), 5.10 (d, J = 5.0 Hz, 1 H), 4.82 (dd, J = 17.6, 1.8 Hz, 1 H), 4.77–4.70 (m, 1 H), 4.40 (d, J = 12.1 Hz, 1 H), 4.27 (s, 1 H), 4.00 (tt, J = 9.6, 4.5 Hz, 1 H), 3.76 (d, J = 12.1 Hz, 1 H), 3.33 (d, J = 4.1 Hz, 1 H), 3.14 (dd, J = 11.1, 8.5 Hz, 1 H), 2.21–2.16 (m, 1 H), 2.12 (ddt, J = 15.1, 11.4, 5.0 Hz, 2 H), 2.07–2.03 (m, 1 H), 1.93–1.82 (m, 3 H), 1.70–1.63 (m, 1 H), 1.62–

1.53 (m, 3 H), 1.51–1.37 (m, 3 H), 1.34 (s, 3 H), 1.29 (s, 3 H), 1.19 (m, 1 H), 1.14 (s, 3 H), 0.90 (t, *J* = 7.8 Hz, 3 H), 0.69 (q, *J* = 7.9 Hz, 2 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 176.8, 117.4, 102.0, 85.2, 73.7, 71.6, 69.4, 67.2, 64.7, 59.8, 49.4, 48.8, 48.6, 46.2, 41.3, 41.2, 36.6, 35.1, 33.4, 32.2, 24.7, 24.0, 23.2, 21.6, 19.9, 7.9.



Fluoride 63: Iron(III) oxalate hexahydrate (68 mg, 0.14 mmol, 4.0 equiv) was stirred in H_2O (2.8 mL) until it completely dissolved (approximately 2 h). The clear yellow solution was degassed by bubbling argon for 10 min and then cooled to 0 ºC. Selectfluor® (50 mg, 0.14 mmol, 4.0 equiv) was added to the reaction mixture, followed by MeCN (4.2 mL). A solution of **61** (15 mg, 0.035 mmol, 1.0 equiv) in THF (1.4 mL) was added to the mixture at 0 ºC, followed by $NaBH_4$ (8.4 mg, 0.224 mmol, 6.4 equiv). After 5 min, the mixture was treated with an additional portion of $NaBH_4$ (8.4 mg). The mixture was stirred for 15 min before being quenched by addition of 30% aqueous NH_4OH (2 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel chromatography (1:4 to 2:3 EtOAc:hexanes) afforded **63** (8 mg, 51%) as a white solid.

Physical state: white solid (m.p. 98–100 ºC).

R$_f$ = 0.40 (silica gel, 3:2 EtOAc:hexanes).

HRMS (*m/z*): calcd for $C_{24}H_{36}BFO_6$, $[M+H]^+$, 451.2662; found, 451.2673.

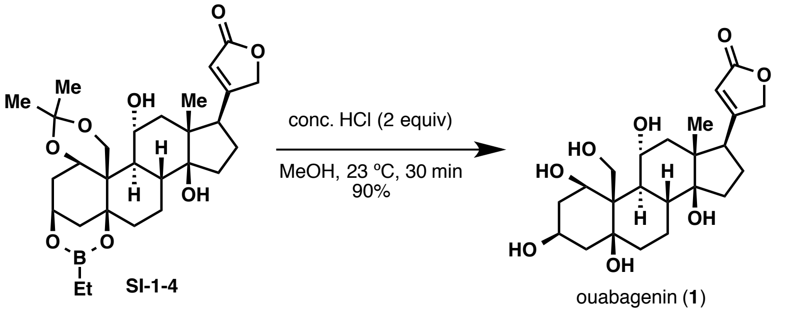
[α]$_D$ = +12.0° (*c* = 0.5, CH_2Cl_2).

IR (film) ν_{max}: 3441, 2936, 2875, 1742, 1403, 1379, 1334, 1291, 1224, 1207, 1057.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.04 (m, 1 H), 4.42 (d, *J* = 12.2 Hz, 1 H), 4.28 (t, *J* = 3.0 Hz, 1 H), 4.12 (ddd, *J* = 14.8, 8.4, 3.7 Hz, 1 H), 3.77 (d, *J* = 12.2 Hz, 1 H), 2.56 –2.40 (m, 2 H), 2.27–2.13 (m, 3 H), 2.11–2.01 (m, 1 H), 1.93–1.78 (m, 3 H), 1.68 (dt, *J* = 13.7, 4.1 Hz, 1 H), 1.62–1.40 (m, 9 H), 1.35 (s, 3 H), 1.29 (s, 3 H), 0.90 (t, *J* = 7.7 Hz, 3 H), 0.70 (q, *J* = 7.7 Hz, 2 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 218.0, 105.0 (d, *J* = 181.2 Hz), 102.0, 71.5, 68.8, 67.0, 64.7, 52.8 (d, *J* = 21.4 Hz), 48.8, 45.9 (d, *J* = 8.0 Hz), 41.0 (d, *J* = 6.7 Hz), 38.9 (d, *J* = 22.0 Hz), 36.2, 35.1, 33.3 (d, *J* = 9.1 Hz), 26.1 (d, *J* = 25.7 Hz), 24.0, 23.2, 20.2 (d, *J* = 3.0 Hz), 14.5 (d, *J* = 9.0 Hz), 7.8.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –156.8.



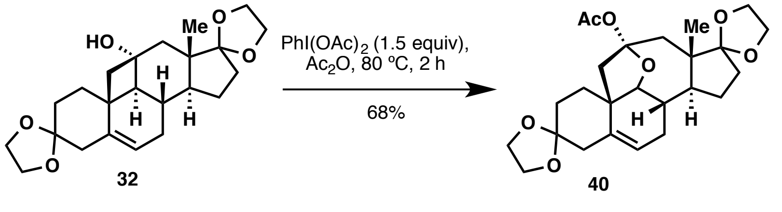
Ouabagenin (1). To a solution of **SI-1-4** (10 mg, 19.4 μmol) in MeOH (200 μL) was added a stock solution of conc. HCl in MeOH (0.8 M, 50 μL, 2.0 equiv) at rt. After 30 min, the mixture was neutralized with solid Na_2CO_3, filtered through Celite® pad and concentrated *in vacuo* and then purified by silica gel chromatography (1:10 to 1:4 MeOH:CH_2Cl_2) to afford ouabagenin (7.6 mg, 90%) as a white solid. This synthetic ouabagenin was found to match spectroscopically with authentic ouabagenin obtained from degradation of ouabain (see SI-Spectra file).

$[\alpha]_D$ = –11.1° (*c* = 0.5, 2:1 $(CD_3)_2SO$:$CDCl_3$).

$[\alpha]_D$ (from degradation) = –8.8° (*c* = 0.5, 2:1 $(CD_3)_2SO$:$CDCl_3$) [lit **$[\alpha]_D$** = +11.32° (*c* = 1.27, H_2O)].

^{1}H NMR (600 MHz, 2:1 $(CD_3)_2SO$:$CDCl_3$): δ 5.84 (s, 1 H), 4.92 (d, *J* = 18.4 Hz, 1 H), 4.81 (dd, *J* = 18.4, 1.8 Hz, 1 H), 4.41 (s, 1 H), 4.21 (d, *J* = 10.4 Hz, 1 H), 4.20–4.10 (m, 1 H), 3.98 (d, *J* = 10.4 Hz, 1 H), 2.83 (t, *J* = 7.1 Hz, 1 H), 2.03–1.93 (m, 3 H), 1.92–1.85 (m, 1 H), 1.82–1.72 (m, 2 H), 1.61 (dd, *J* = 11.4, 8.6 Hz, 1 H), 1.56 (dd, *J* = 13.5, 4.5 Hz, 1H), 1.49–1.40 (m, 1 H), 1.37–1.28 (m, 2 H), 1.22 (s, 1 H), 1.11 (s, 1 H), 0.81 (s, 3 H).

^{13}C NMR (2:1 $(CD_3)_2SO$:$CDCl_3$, 151 MHz): 175.0, 173.5, 116.3, 83.5, 75.1, 72.9, 66.2, 65.4, 60.6, 49.7, 49.0, 48.6, 48.4, 47.2, 40.1, 32.3, 26.0, 22.7, 16.9.



Ketal 40: To a solution of **32** (10 mg, 0.0258 mmol) in Ac_2O (0.25 mL) was added $PhI(OAc)_2$ (12.8 mg, 0.0386 mmol, 1.5 equiv). The solution was then heated at 80 ºC for 2 h, upon which TLC analysis showed that all starting material had been consumed. The reaction mixture was concentrated *in vacuo* (with azeotropic removal of acetic acid using additional toluene) and then purified by silica gel chromatography (3:7 EtOAc:hexanes) to afford hemiketal **40** (8 mg, 68%) as a white solid.

Physical state: white solid.

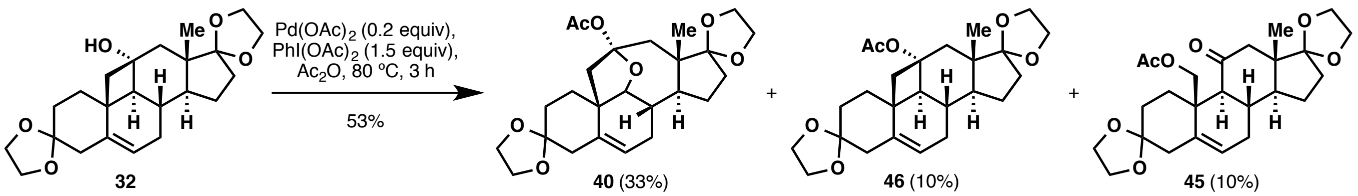
R_f = 0.13 (silica gel, 1:4 EtOAc:hexanes).

HRMS (*m*/*z*): calcd for $C_{25}H_{34}O_7$, $[M+H]^+$, 447.2383; found, 447.2386.

IR (film) ν_{max}: 2974, 2944, 2882, 1733, 1442, 1369, 1255, 1112, 1099, 1079, 1011, 960.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.71–5.53 (m, 1 H), 4.03–3.74 (m, 8 H), 3.44 (d, *J* = 8.3 Hz, 1 H), 2.63 (dt, *J* = 12.1, 7.7 Hz, 1 H), 2.55 (d, *J* = 14.6 Hz, 1 H), 2.35 (d, *J* = 14.6 Hz, 1H), 2.30 (dd, *J* = 13.8, 2.8 Hz, 1 H), 2.22 (dd, *J* = 13.7, 2.5 Hz, 1 H), 2.17 (d, *J* = 13.6 Hz, 1 H), 2.13 (d, *J* = 13.6 Hz, 1 H), 2.05 (s, 3H), 2.00 (dt, *J* = 13.2, 3.3 Hz, 1 H), 1.96–1.87 (m, 3 H), 1.85 (dd, *J* = 9.2, 6.3 Hz, 2 H), 1.74 (dd, *J* = 13.2, 3.1 Hz, 1 H), 1.67–1.39 (m, 5 H), 1.04 (s, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 169.8, 139.2, 127.9, 118.7, 113.7, 109.3, 86.9, 65.1, 64.7, 64.6, 64.4, 51.0, 50.9, 46.8, 43.4, 40.6, 39.0, 38.8, 33.7, 33.4, 31.4, 29.0, 22.3, 20.0, 18.8.



Acetates 45 and **46**: To a solution of **32** (20 mg, 0.0514 mmol) in Ac_2O (1 mL) was added $Pd(OAc)_2$ (2.3 mg, 0.0103 mmol, 0.2 equiv) and $PhI(OAc)_2$ (24.8 mg, 0.0771 mmol, 1.5 equiv). The solution was then heated at 80 ºC for 3 h, upon which TLC analysis showed that all starting material had been consumed. The reaction mixture was concentrated *in vacuo* (with azeotropic removal of acetic acid using additional toluene) and then purified by preparative TLC (1:9 EtOAc:CH_2Cl_2) to afford acetate **46** (2.1 mg, 10%), hemiketal **40** (7.5 mg, 33%), and acetate **45** (2.2 mg, 10%).

Spectroscopic data for **46**:

Physical state: white foam.

R_f = 0.23 (silica gel, 1:4 EtOAc:hexanes).

HRMS (*m*/*z*): calcd for $C_{25}H_{34}O_6$, $[M–OAc]^+$, 371.2222; found, 371.2211.

IR (film) ν_{max}: 2951, 2880, 1729, 1434, 1368, 1296, 1247, 1170, 1122, 1077, 1041, 1014.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.66 (d, *J* = 6.7 Hz, 1 H), 4.00–3.73 (m, 8 H), 2.64 (d, *J* = 13.0 Hz, 1 H), 2.51 (dd, *J* = 13.0, 4.2 Hz, 1 H), 2.30 (dt, *J* = 13.3, 3.4 Hz, 1 H), 2.22–2.15 (m, 2 H), 2.03 (s, 3 H), 1.95 (ddd, *J* = 14.7, 11.6, 3.3 Hz, 1 H), 1.91–1.57 (m, 10 H), 1.42–1.32 (m, 1 H), 1.02 (s, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 170.5, 140.8, 126.4, 118.7, 109.4, 98.2, 85.8, 65.2, 64.7, 64.6, 64.5, 54.8, 49.5, 44.0, 43.6, 42.4, 41.8, 38.3, 37.8, 34.7, 34.7, 32.1, 26.9, 22.8, 20.8, 17.6.

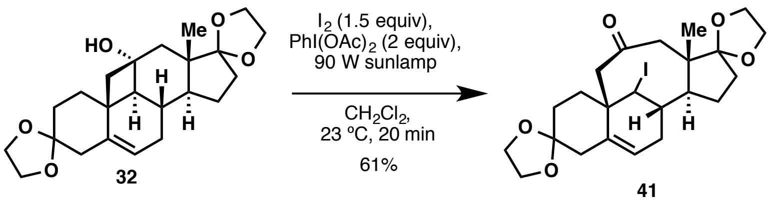
Spectroscopic data for **45**:

Physical state: white foam.

R$_f$ = 0.11 (silica gel, 1:4 EtOAc:hexanes).

HRMS (*m/z*): calcd for $C_{25}H_{34}O_7$, $[M+H]^+$, 447.2383; found, 447.2387.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.58 (d, *J* = 5.4 Hz, 1 H), 4.78 (d, *J* = 11.5 Hz, 1 H), 4.60 (d, *J* = 11.4 Hz, 1 H), 4.01–3.81 (m, 8 H), 2.69–2.64 (m, 1 H), 2.62 (d, *J* = 13.5 Hz, 1 H), 2.57 (dt, *J* = 13.9, 3.8 Hz, 1 H), 2.26 (qd, *J* = 10.9, 5.1 Hz, 1 H), 2.18–2.13 (m, 1 H), 2.17 (d, *J* = 11.7 Hz, 1 H), 2.12–2.01 (m, 2 H), 1.98 (s, 3 H), 1.96–1.80 (m, 5 H), 1.77 (td, *J* = 14.3, 4.3 Hz, 1 H), 1.40–1.26 (m, 2 H), 0.88 (s, 3 H).



Iodide 41: To a solution of **32** (10 mg, 0.0257 mmol) in CH_2Cl_2 (0.5 mL) was added sequentially $PhI(OAc)_2$ (16.8 mg, 0.0515 mmol, 2.0 equiv) and I_2 (9.8 mg, 0.0386 mmol, 1.5 equiv) at room temperature. The resulting suspension was irradiated with sunlamp (90 W, 6 inches from the walls of the flask) for 20 min. Irradiation was then halted and the crude mixture was washed with sat. aq. $Na_2S_2O_3$ (2.5 mL) until colorless. The aqueous layer was back-extracted twice with EtOAc (2 x 2.5 mL) and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting yellow oil was purified by silica gel chromatography (1:4 EtOAc:hexanes) to give pure **41** (8.0 mg, 61%) as a white soild.

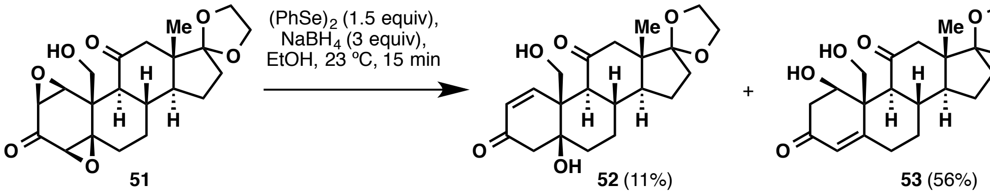
Physical state: white solid.

R$_f$ = 0.42 (silica gel, 2:3 EtOAc:hexanes).

HRMS (*m/z*): calcd for $C_{23}H_{31}IO_5$, $[M+H]^+$, 515.1289; found, 515.1293.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.76–5.65 (m, 1 H), 4.91 (s, 1 H), 4.07–3.79 (m, 8 H), 3.15 (d, *J* = 12.5 Hz, 1 H), 2.86 (d, *J* = 11.8 Hz, 1 H), 2.49 (dt, *J* = 14.5, 2.7 Hz, 1 H), 2.44–2.40 (m, 1H), 2.37 (d, *J* = 12.5 Hz, 1 H), 2.27 (dd, *J* = 14.6, 2.5 Hz, 1 H), 2.18–2.08 (m, 2 H), 2.07–1.87 (m, 4 H), 1.67–1.59 (m, 3 H), 1.49–1.35 (m, 2 H), 0.93 (s, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 210.0, 136.7, 128.6, 117.1, 108.6, 65.5, 64.8, 64.6, 64.3, 59.9, 57.2, 56.8, 50.7, 49.7, 47.5, 43.7, 41.9, 41.3, 36.1, 33.0, 31.3, 20.4, 14.9.



Enone 53: To a solution of $(PhSe)_2$ (62.4 mg, 0.2 mmol) in EtOH (1 mL) was added $NaBH_4$ (15 mg, 0.397 mmol, ca. 2.0 equiv relative to $(PhSe)_2$) upon which vigorous bubbling was observed. After the solution turned colorless, 400 µL of this stock solution (ca. 3 equiv relative to **51**) was added to a solution of **51** (10 mg, 0.0256 mmol) in EtOH (125 µL) at room temperature. After 15 min, H_2O (3 mL) was added to the reaction, followed by EtOAc (3 mL). The aqueous phase was extracted with EtOAc (2 x 2.5 mL) and the combined organic portions were washed with brine (3 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified by preparative TLC (3:1 EtOAc:hexanes) to afford enones **52** (1.1 mg, 11%) and **53** (5.4 mg, 56%).

Spectroscopic data for **53**:

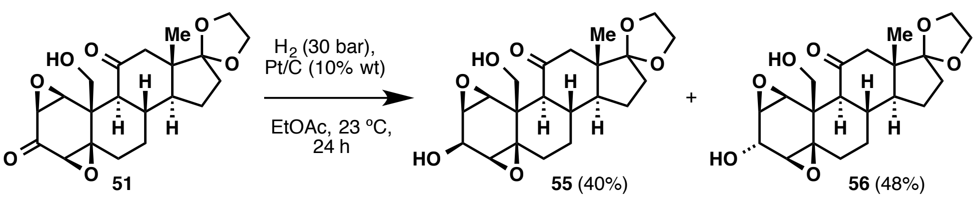
Physical state: white foam.

R$_f$ = 0.26 (silica gel, 3:1 EtOAc:hexanes).

HRMS (*m*/*z*): calcd for $C_{21}H_{28}O_6$, $[M+H]^+$, 377.1964; found, 377.1969.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.98 (d, *J* = 1.4 Hz, 1 H), 4.64 (d, *J* = 3.1 Hz, 1 H), 4.41 (dd, *J* = 11.8, 3.2 Hz, 1 H), 4.34–4.27 (m, 1 H), 3.97–3.79 (m, 5 H), 2.77 (d, *J* = 12.1 Hz, 1 H), 2.68 (dd, *J* = 16.2, 8.1 Hz, 1 H), 2.58 (dd, *J* = 16.1, 4.5 Hz, 1 H), 2.46–2.39 (td, *J* = 13.4, 4.4 Hz, 1H), 2.38 (dt, *J* = 3.1, 1.7 Hz, 1 H), 2.35 (d, *J* = 10.6 Hz, 1 H), 2.20 (d, *J* = 12.0 Hz, 1 H), 2.14–1.91 (m, 5 H), 1.81 (dddd, *J* = 13.1, 10.1, 6.9, 3.4 Hz, 1 H), 1.39 (dtd, *J* = 24.1, 12.4, 6.1 Hz, 1 H), 1.32–1.22 (m, 1 H), 0.86 (s, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 215.2, 197.3, 163.0, 126.1, 117.2, 71.5, 65.6, 64.7, 62.9, 62.7, 50.0, 49.9, 49.5, 48.6, 43.0, 38.6, 34.3, 33.4, 32.8, 22.1, 15.1.



Diols 55 and 56: To a vial containing diepoxide **51** (25 mg, 0.064 mmol) was added 10% Pt/C (3 mg) and EtOAc (0.5 mL). This vial was placed inside a bomb reactor, which was then charged with H_2 gas (30 bar). After 24 h, the reactor was vented, and the reaction mixture was filtered through a pad of Celite®, which was washed with EtOAc. The resulting colorless solution was concentrated *in vacuo* and the crude mixture was purified by preparative TLC (EtOAc) to afford diols **55** (10 mg, 40%) and **56** (12 mg, 48%) as white solids.

Spectroscopic data for **55**:

Physical state: white solid.

R_f = 0.15 (silica gel, EtOAc).

HRMS (*m*/*z*): calcd for $C_{21}H_{28}O_7$, $[M+H]^+$, 393.1913; found, 393.1915.

IR (film) ν_{max}: 3452, 2944, 2881, 1702, 1459, 1311, 1173, 1101, 1054, 937, 917.

^{1}H NMR (600 MHz, CDCl$_3$): δ 4.63 (s, 1 H), 4.46 (d, *J* = 11.5 Hz, 1 H), 4.17 (d, *J* = 11.5 Hz, 1 H), 4.00–3.78 (m, 4 H), 3.60 (d, *J* = 3.6 Hz, 1 H), 3.05 (s, 1 H), 2.82 (s, 1 H), 2.80 (d, *J* = 11.8 Hz, 1 H), 2.54 (d, *J* = 11.3 Hz, 1 H), 2.16 (d, *J* = 11.7 Hz, 1 H), 2.14–2.03 (m, 3H), 1.99–1.88 (m, 3 H), 1.81 (dddd, *J* = 12.9, 10.2, 7.3, 3.4 Hz, 1 H), 1.38 (tt, *J* = 12.2, 6.0 Hz, 1 H), 1.35–1.22 (m, 1 H), 1.04 (dt, *J* = 13.7, 3.4 Hz, 1 H), 0.85 (s, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 212.5, 117.5, 65.6, 64.8, 63.4, 62.5, 62.1, 59.7, 59.4, 54.6, 52.1, 50.2, 50.0, 49.5, 40.5, 37.9, 34.4, 31.6, 30.1, 22.1, 15.0.

Spectroscopic data for **56**:

Physical state: white solid.

R_f = 0.09 (silica gel, EtOAc).

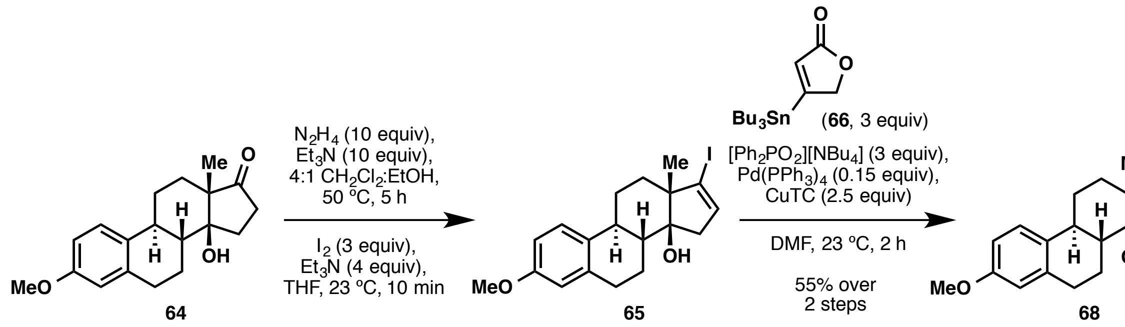
HRMS (*m*/*z*): calcd for $C_{21}H_{28}O_7$, $[M+H]^+$, 393.1913; found, 393.1916.

IR (film) ν_{max}: 3445, 2942, 2880, 1702, 1459, 1311, 1170, 1101, 1046, 916.

^{1}H NMR (600 MHz, CDCl$_3$): δ 4.40 (d, *J* = 11.6 Hz, 1 H), 4.15 (t, *J* = 3.0 Hz, 1 H), 4.12 (d, *J* = 11.6 Hz, 1 H), 3.91–3.72 (m, 4 H), 3.69 (d, *J* = 4.0 Hz, 1 H), 3.14 (dt, *J* = 4.1, 2.6 Hz, 1 H), 2.93 (t, *J* = 2.7 Hz, 1 H), 2.69 (d, *J* = 11.8 Hz, 1 H), 2.16 (d, *J* = 11.2 Hz, 1 H), 2.10 (d, *J* = 11.7 Hz, 1 H), 2.06 (td, *J* = 13.9

4.0 Hz, 1 H), 2.02–1.95 (m, 2 H), 1.93–1.82 (m, 3 H), 1.77–1.70 (m, 1 H), 1.31 (qd, *J* = 12.1, 6.2 Hz, 1 H), 1.20–1.10 (m, 2 H), 1.00 (dt, *J* = 13.8, 3.3 Hz, 1 H), 0.78 (s, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 211.8, 117.4, 67.5, 65.6, 64.8, 64.8, 63.2, 60.7, 59.7, 59.4, 53.2, 50.2, 50.0, 49.8, 40.1, 37.9, 34.4, 31.7, 30.2, 22.1, 15.0.



Ketone 64: The procedure outlined for the synthesis of **62** from **60** was employed for the preparation of **64** from methoxyestrone.

Physical state: white foam.

R$_f$ = 0.11 (silica gel, 1:4 EtOAc:hexanes).

HRMS (*m/z*): calcd for $C_{19}H_{24}O_3$, [M–OH]$^+$, 283.1698; found, 283.1691.

IR (film) $\nu_{\max}$: 3489, 2932, 2863, 2837, 1726, 1609, 1499, 1465, 1269, 1253, 1236, 1052, 1039.

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.20 (d, *J* = 8.7 Hz, 1 H), 6.74 (dd, *J* = 8.7, 2.9 Hz, 1 H), 6.66 (d, *J* = 2.8 Hz, 1 H), 3.78 (s, 3 H), 2.99–2.84 (m, 2 H), 2.63–2.57 (m, 1 H), 2.51–2.45 (m, 2 H), 2.33 (dq, *J* = 13.3, 3.6 Hz, 1 H), 2.25–2.20 (m, 2 H), 1.88 (ddd, *J* = 13.8, 6.8, 4.3 Hz, 1 H), 1.65–1.47 (m, 4 H), 1.45–1.36 (m, 2 H), 1.09 (s, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 221.2, 157.8, 137.7, 131.4, 126.9, 113.9, 112.1, 82.0, 55.4, 53.6, 45.1, 40.1, 33.4, 32.3, 30.5, 26.9, 25.8, 22.2, 13.1.

Dienoate 68: To a solution of **64** (20 mg, 66.6 μmol) in EtOH (1.2 mL) was added anhydrous N_2H_4 (21 μL, 666 μmol, 10.0 equiv) and Et_3N (93 μL, 666 μmol, 10.0 equiv). The mixture was heated at 50 ºC for 5 h, after which the reaction was allowed to cool and concentrated *in vacuo*. The residue thus obtained was dissolved in degassed THF (1.4 mL), upon which Et_3N (37 μL, 266 μmol, 4.0 equiv) was added. A stock solution of I_2 (51 mg, 200 μmol, 3.0 equiv) in THF (0.4 mL) was prepared and added dropwise to the reaction mixture. After the solution stayed brown for more than 30 s, addition was halted and stirring was continued for 10 min. The reaction was then diluted with EtOAc (5 mL) and washed with sat. aq. $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic portions were washed with sat. aq. NaCl (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was passed through a short pad of silica gel, which was washed with 1:1 hexanes:EtOAc. Concentration *in vacuo* afforded vinyl iodide **65**, which was used for the next step without further purification.

Iodide **65** and stannane **66** (75 mg, 201 μmol, 3.0 equiv) were dissolved in DMF (1 mL) and the resulting solution was degassed by bubbling argon for 15 min. To this solution was sequentially added $[Ph_2PO_2][NBu_4]$ (91 mg, 200 µmol, 3.0 equiv), $Pd(PPh_3)_4$ (11.6 mg, 10 µmol, 0.15 equiv) and CuTC (32 mg, 167 µmol, 2.5 equiv). The reaction mixture was then stirred for 2 h and then quenched with water (2.5 mL). The suspension was passed through a pad of Celite®, which was washed with EtOAc (10 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic layers were successively washed with sat. aq. $NaHCO_3$ (10 mL), H_2O (2 x 5 mL) and sat. aq. NaCl (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (3:1 to 1:1 EtOAc:hexanes) afforded dienoate **68** (13.4 mg, 55% over 2 steps) as a white foam.

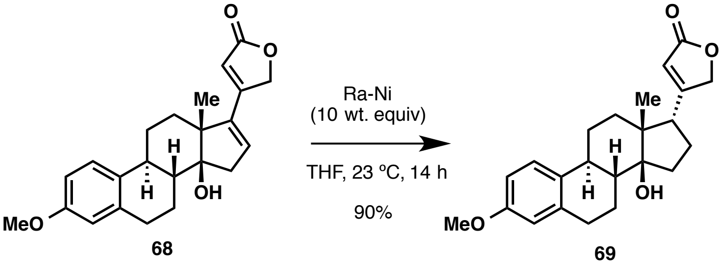
Physical state: white foam.

$\boldsymbol{R_f}$ = 0.59 (silica gel, 3:2 EtOAc:hexanes).

HRMS (*m/z*): calcd for $C_{23}H_{26}O_4$, $[M+H]^+$, 367.1909; found, 367.1918.

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.24 (d, *J* = 8.8 Hz, 1 H), 6.74 (dd, *J* = 8.7, 2.8 Hz, 1 H), 6.66 (d, *J* = 2.6 Hz, 1 H), 6.16 (s, 1 H), 6.01 (s, 1 H), 5.03 (d, *J* = 16.3 Hz, 1 H), 4.97 (d, *J* = 16.3 Hz, 1 H), 2.96–2.87 (m, 2 H), 2.76 (d, *J* = 18.6 Hz, 1 H), 2.49 (t, *J* = 11.7 Hz, 1 H), 2.42 (dd, *J* = 17.9, 2.7 Hz, 1 H), 2.32–2.22 (m, 2 H), 2.17 (d, *J* = 13.8 Hz, 1 H), 1.67 (t, *J* = 11.6 Hz, 1 H), 1.50–1.31 (m, 3 H), 1.33 (s, 3H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 174.5, 158.4, 157.8, 143.9, 137.9, 132.6, 131.1, 127.3, 113.9, 112.7, 112.1, 84.9, 71.8, 55.4, 52.5, 44.5, 40.4, 40.0, 38.7, 30.6, 25.9, 23.6, 16.8.



Enoate 69: For this procedure, Raney nickel (1.0 g) was washed with H_2O (3 x 5 mL), sat. aq. Rochelle's salt (3 x 5 mL), H_2O (5 x 5 mL), MeOH (3 x 5 mL), and H_2O (3 x 5 mL), after which it was stored under H_2O (10 mL). To dienoate **68** (4 mg, 0.011 mmol) in THF (0.4 mL) was added the washed Raney nickel

(40 mg, 10 wt. equiv, which includes water). The heterogeneous mixture was stirred at room temperature for 14 h, at which point NMR analysis showed that all starting material had been completely consumed. The mixture was filtered through a pad of Celite®, which was washed with EtOAc, and then concentrated *in vacuo*. The crude reaction mixture was purified by preparative TLC (1:1 EtOAc:hexanes) to afford enoate **69** (3.6 mg, 90%) as a white foam.

Physical state: white foam;

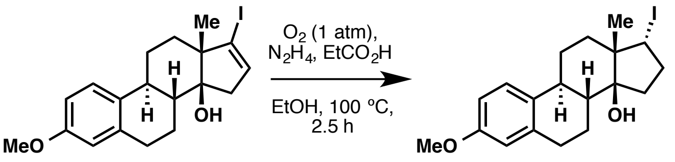
R$_f$ = 0.59 (silica gel, 3:2 EtOAc:hexanes);

HRMS (*m/z*): calcd for $C_{23}H_{28}O_4$, $[M+H]^+$, 369.2066; found, 369.2070;

IR (film) ν_{max}: 3465, 2927, 2863, 1781, 1737, 1621, 1499, 1258, 1234, 1036, 905;

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.19 (d, *J* = 8.6 Hz, 1 H), 6.73 (dd, *J* = 8.7, 2.8 Hz, 1 H), 6.64 (d, *J* = 2.8 Hz, 1 H), 5.93 (d, *J* = 1.7 Hz, 1 H), 4.86 (dd, *J* = 17.6, 1.8 Hz, 1 H), 4.77 (dd, *J* = 17.6, 1.8 Hz, 1 H), 3.78 (s, 3 H), 3.24 (t, *J* = 9.7 Hz, 1 H), 2.92–2.86 (m, 2 H), 2.54–2.44 (m, 1 H), 2.31–2.24 (m, 1 H), 2.23–2.12 (m, 3 H), 1.91–1.81 (m, 1 H), 1.67 (ddd, *J* = 15.7, 10.3, 4.6 Hz, 1 H), 1.49–1.29 (m, 4 H), 1.08 (s, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 174.1, 171.2, 157.7, 137.7, 131.5, 126.9, 117.0, 113.8, 112.0, 85.5, 73.9, 55.37, 49.1, 48.3, 45.2, 40.00, 31.2, 30.7, 30.6, 26.1, 24.8, 23.3, 18.5.



65 **71**

Iodide 71: To a solution of vinyl iodide **65** (10 mg, 0.0243 mmol), N_2H_4 (25 µL), and $EtCO_2H$ (20 µL) in EtOH (0.5 mL) was saturated with O_2 gas via bubbling over a period of 15 min. The resulting solution was refluxed for 2.5 h. After cooling, the crude mixture was concentrated *in vacuo*, redissolved in CH_2Cl_2 (7.5 mL), and washed with H_2O (2.5 mL) and then brine (2.5 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford **71** as a white foam. This material was used for the next step without further purification.

Physical state: white foam;

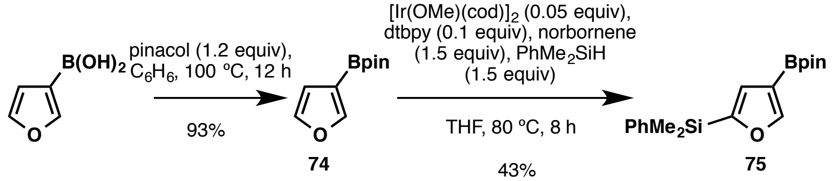
R$_f$ = 0.59 (silica gel, 3:2 EtOAc:hexanes);

HRMS (*m/z*): calcd for $C_{19}H_{25}IO_2$, $[M+H]^+$, 413.0978; found, 413.0980;

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.22 (d, *J* = 8.6 Hz, 1 H), 6.74 (dd, *J* = 8.7, 2.8 Hz, 1 H), 6.64 (d, *J* = 2.8 Hz, 1 H), 4.46 (t, *J* = 9.6 Hz, 1 H), 3.78 (s, 3 H), 2.95–2.81 (m, 2 H), 2.50 (dtd, *J* = 14.3, 9.6, 4.9 Hz, 1

H), 2.43 (dt, J = 10.9, 5.5 Hz, 1 H), 2.30–2.17 (m, 3 H), 2.07 (ddd, J = 14.4, 12.3, 5.0 Hz, 1 H), 1.65 (dd, J = 10.6, 3.3 Hz, 1 H), 1.60 (ddd, J = 14.5, 9.9, 4.7 Hz, 1 H), 1.50 (td, J = 11.5, 2.1 Hz, 1 H), 1.45–1.37 (m, 1 H), 1.34 (td, J = 7.0, 3.9 Hz, 1 H), 0.99 (s, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 157.8, 137.8, 131.8, 126.9, 113.8, 112.0, 80.6, 55.4, 48.5, 45.9, 42.5, 40.3, 35.0, 32.7, 32.2, 30.7, 26.7, 23.0, 16.6.



Furan 74: To a solution of 2-furanboronic acid (1.00 g, 8.94 mmol) in benzene (30 mL) was added pinacol (1.27 g, 10.73 mmol, 1.2 equiv). The reaction vessel was incorporated into a standard Dean-Stark setup and immersed in an oil bath preheated to 110 ºC and stirred vigorously. After 12 h, the reaction was lifted out of the oil bath and allowed to cool. The crude mixture was concentrated *in vacuo*, and purified by silica gel chromatography (20:1 to 10:1 EtOAc:hexanes) to afford **74** (1.61 g, 93%) as a white solid.

Physical state: white solid;

R$_f$ = 0.41 (silica gel, 10:1 EtOAc:hexanes);

IR (film) ν_{max}: 2979, 2933, 1570, 1504, 1373, 1347, 1306, 1141, 1066;

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.78 (dd, J = 1.4, 0.8 Hz, 1 H), 7.46 (t, J = 1.6 Hz, 1 H), 6.59 (dd, J = 1.8, 0.8 Hz, 1 H), 1.31 (s, 12 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 151.3, 143.0, 113.2, 83.6, 24.9.

Silylfuran 75: A flame-dried pressure vessel was charged with furan **74** (70 mg, 0.361 mmol), [Ir(OMe)(cod)]$_2$ (12 mg, 0.018 mmol, 0.05 equiv), and dtbpy (10 mg, 0.036 mmol, 0.1 equiv), and then evacuated and flushed with argon three times. Under a positive flow of argon, 2-norbornene (51 mg, 0.541 mmol, 1.5 equiv) and degassed THF (1.8 mL) were added. After stirring for 5 min, PhMe$_2$SiH (86 μL, 0.541 mmol, 1.5 equiv) was added dropwise and the reaction mixture was heated at 80 ºC for 8 h. The mixture was concentrated *in vacuo*, and the crude product was purified by silica gel chromatography (1:40 Et$_2$O:hexanes) to afford furan **75** (51 mg, 43%) as a white solid.

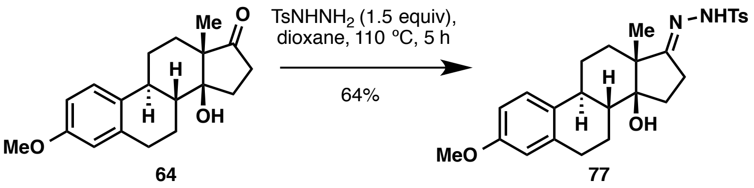
Physical state: white solid;

R$_f$ = 0.18 (silica gel, 40:1 Et$_2$O:hexanes);

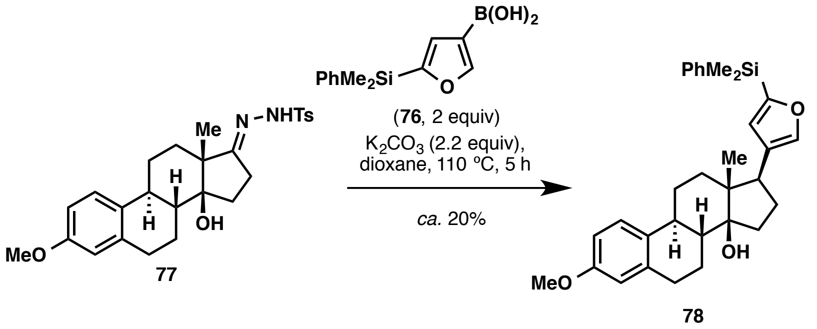
IR (film) ν_{max}: 2978, 2932, 1573, 1479, 1372, 1325, 1193, 1143, 1105, 969;

^{1}H NMR (600 MHz, CDCl$_3$): δ 8.02 (s, 1 H), 7.60–7.51 (m, 2 H), 7.43–7.32 (m, 3 H), 6.91 (s, 1 H), 1.33 (d, J = 8.3 Hz, 12 H), 0.55 (s, 6 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 158.9, 155.8, 134.0, 129.5, 128.0, 125.1, 83.6, 24.9, –2.8.

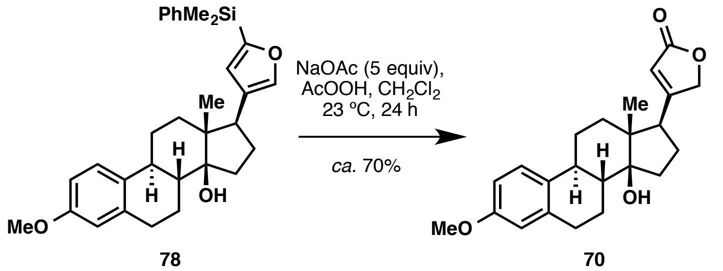


Hydrazone 77: A mixture of ketone **64** (10 mg, 0.0333 mmol) and TsNHNH$_2$ (9.4 mg, 0.050 mmol, 1.5 equiv) was heated in dioxane (0.4 mL) at 110 ºC. After 5 h, the reaction was allowed to cool, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (1:1 EtOAc:hexanes) to afford hydrazone **77** (10 mg, 64%) as a white solid.



Estrone-furan adduct 78:

A mixture of hydrazone **77** (10 mg, 0.0213 mmol), boronic acid **76** (10.5 mg, 0.0426 mmol, 2 equiv) (**76** was prepared from furan **75** according to Hartwig's procedure[2]), and K$_2$CO$_3$ (6.5 mg, 0.0469 mmol, 2.2 equiv) in dioxane (0.3 mL) was heated at 110 ºC for 5 h. The reaction mixture was allowed to cool, filtered through a pad of Celite®, and concentrated *in vacuo*. Purification by preparative TLC (4:1 EtOAc:hexanes) afforded adduct **78** (2.1 mg, 20%).



Butenolide 70: To a solution of **78** (2.1 mg, 0.0043 mmol) in CH_2Cl_2 (0.3 mL) was added solid NaOAc (1.7 mg, 0.0205 mmol, ca. 5.0 equiv) and a 32% wt. solution of AcOOH (5 µL). The resulting solution was stirred at room temperature for 24 h and then quenched with sat. aq. $Na_2S_2O_3$ (2.5 mL). The aqueous phase was extracted with EtOAc (3 x 2.5 mL) and the combined organic portions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by preparative TLC (1:1 EtOAc:hexanes) afforded butenolide **70** (1.1 mg, 70%) as a white foam.

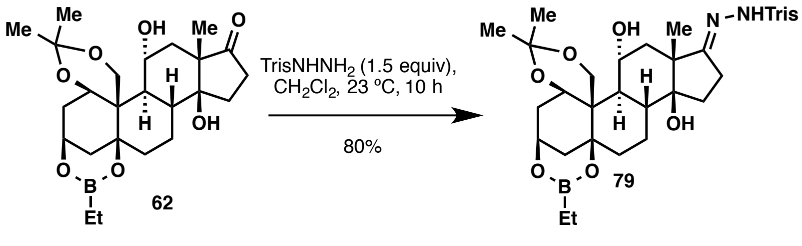
Physical state: white foam;

R_f = 0.59 (silica gel, 3:2 EtOAc:hexanes);

HRMS (*m/z*): calcd for $C_{23}H_{28}O_4$, $[M+H]^+$, 369.2066; found, 369.2071;

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.19 (d, *J* = 8.6 Hz, 1 H), 6.73 (dd, *J* = 8.7, 2.8 Hz, 1 H), 6.64 (d, *J* = 2.7 Hz, 1 H), 5.92 (d, *J* = 1.9 Hz, 1 H), 5.00 (dd, *J* = 18.0, 1.8 Hz, 1 H), 4.84 (dd, *J* = 17.9, 1.9 Hz, 1 H), 3.78 (s, 3 H), 2.96–2.81 (m, 3 H), 2.55 (t, *J* = 11.6 Hz, 1 H), 1.94 (ddt, *J* = 18.4, 8.8, 4.5 Hz, 1 H), 1.75–1.67 (m, 2 H), 1.63 (td, *J* = 13.7, 4.0 Hz, 1 H), 1.51–1.41 (m, 3 H), 1.26–1.22 (m, 2 H), 0.92 (s, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 174.5, 174.4, 157.8, 137.6, 131.7, 126.9, 118.0, 113.8, 112.1, 85.0, 73.6, 55.4, 50.8, 49.9, 45.5, 40.3, 39.9, 32.7, 30.7, 27.4, 27.3, 23.8, 16.1.



Hydrazone 79: To a solution of **62** (10 mg, 0.0224 mmol) in CH_2Cl_2 (0.25 mL) was added $TrisNHNH_2$ (10 mg, 0.0336 mmol, 1.5 equiv). The resulting solution was stirred at room temperature under Ar for 10 h. The crude mixture was concentrated *in vacuo*, and purified by flash chromatography (3:2 EtOAc:hexanes) to afford hydrazone **79** (13 mg, 80%) as a white solid.

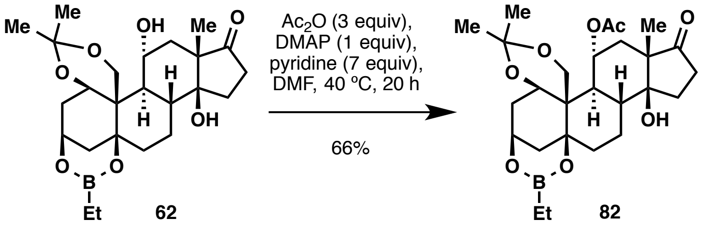
Physical state: white solid;

***R**$_f$* = 0.19 (silica gel, 3:2 EtOAc:hexanes);

HRMS (*m/z*): calcd for $C_{39}H_{61}BN_2O_8S$, $[M+H]^+$, 729.4320; found, 729.4324;

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.18 (s, 1 H), 7.14 (s, 2 H), 5.08 (dd, *J* = 5.4, 1.9 Hz, 1 H), 4.36 (d, *J* = 12.1 Hz, 1 H), 4.24 (dd, *J* = 3.8, 2.1 Hz, 1 H), 4.18 (p, *J* = 6.7 Hz, 2 H), 3.97 (td, *J* = 8.8, 4.5 Hz, 1 H), 3.72 (d, *J* = 12.0 Hz, 1 H), 3.15 (d, *J* = 4.2 Hz, 1 H), 2.90 (p, *J* = 6.9 Hz, 1 H), 2.43–2.28 (m, 2 H), 2.19–2.11 (m, 1 H), 2.11–2.01 (m, 2 H), 1.92–1.77 (m, 3 H), 1.53 (dd, *J* = 13.7, 3.7 Hz, 2 H), 1.48–1.35 (m, 5 H), 1.27–1.21 (m, 20 H), 1.08 (s, 3 H), 0.88 (t, *J* = 7.8 Hz, 3 H), 0.67 (q, *J* = 7.8 Hz, 2 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 167.8, 153.4, 151.4, 131.2, 123.8, 101.9, 82.9, 71.6, 69.4, 67.2, 64.7, 59.8, 50.6, 48.8, 45.9, 44.7, 40.7, 36.7, 35.1, 34.3, 33.3, 30.0, 29.4, 25.0, 24.9, 24.0, 23.7, 23.7, 23.7, 23.2, 21.2, 16.5, 7.8.



Acetate 82: To a solution of **62** (10 mg, 0.0224 mmol) in DMF (0.25 mL) was added Ac_2O (6.4 μL, 0.067 mmol, 3.0 equiv), pyridine (12.6 μL, 0.156 mmol, 7.0 equiv), and DMAP (2.7 mg, 0.0224 mmol, 1.0 equiv). The resulting solution was stirred at 40 ºC for 20 h. The reaction was quenched by addition of H_2O (2.5 mL), and the aqueous phase was extracted with EtOAc (3 x 2.5 mL). The combined organic portions were washed with H_2O (2.5 mL) and brine (2 x 2.5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified by preparative TLC (3:2 EtOAc:hexanes) to afford acetate **82** (7.2 mg, 66%) as a white foam.

Physical state: white foam;

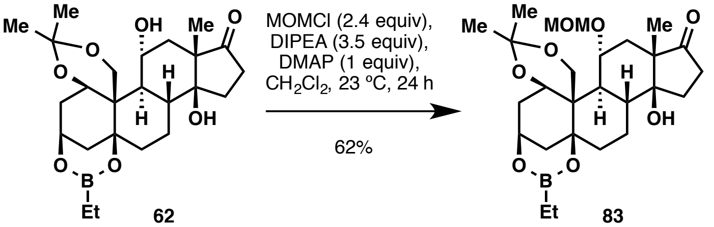
***R**$_f$* = 0.38 (silica gel, 3:2 EtOAc:hexanes);

HRMS (*m/z*): calcd for $C_{26}H_{39}BO_8$, $[M+H]^+$, 491.2816; found, 491.2820;

IR (film) ν_{max}: 3496, 2933, 2876, 1740, 1459, 1378, 1334, 1228, 1207, 1057;

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.32 (td, *J* = 9.0, 4.5 Hz, 1 H), 4.46 (dd, *J* = 5.1, 2.0 Hz, 1 H), 4.33 (d, *J* = 12.4 Hz, 1 H), 4.29 (d, *J* = 3.2 Hz, 1 H), 3.74 (d, *J* = 12.3 Hz, 1 H), 2.54–2.37 (m, 2 H), 2.26–2.15 (m, 3 H), 1.99 (s, 3 H), 2.00–1.96 (m, 1 H), 1.91–1.85 (m, 2 H), 1.83–1.72 (m, 2 H), 1.64 (td, *J* = 12.5, 3.7 Hz, 1 H), 1.56–1.44 (m, 3 H), 1.31 (s, 3 H), 1.19 (s, 3 H), 1.13 (s, 3 H), 0.89 (t, *J* = 7.8 Hz, 3 H), 0.68 (q, *J* = 8.0 Hz, 2 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 218.7, 169.0, 101.5, 80.7, 712.0, 69.4, 66.4, 65.0, 59.8, 52.7, 49.0, 44.1, 41.0, 37.3, 36.8, 345.0, 33.4, 32.9, 27.9, 24.2, 23.0, 21.7, 20.9, 14.8, 7.8.



MOM ether 83: To a solution of **62** (10 mg, 0.0224 mmol) in CH_2Cl_2 (0.25 mL) at 0 ºC was added Hunig's base (14 µL, 0.0804 mmol, ca. 3.5 equiv), MOMCl (4 µL, 0.0527 mmol, ca. 2.4 equiv) and DMAP (2.7 mg, 0.0224 mmol, 1.0 equiv). The reaction was warmed from 0 ºC to room temperature, and stirred for 24 h. MeOH (50 µL) was added, and the reaction mixture was concentrated *in vacuo*, before being purified by preparative TLC (3:2 EtOAc:hexanes) to afford **83** (6.8 mg, 62%) as a white foam.

Physical state: white foam;

R_f = 0.45 (silica gel, 3:2 EtOAc:hexanes);

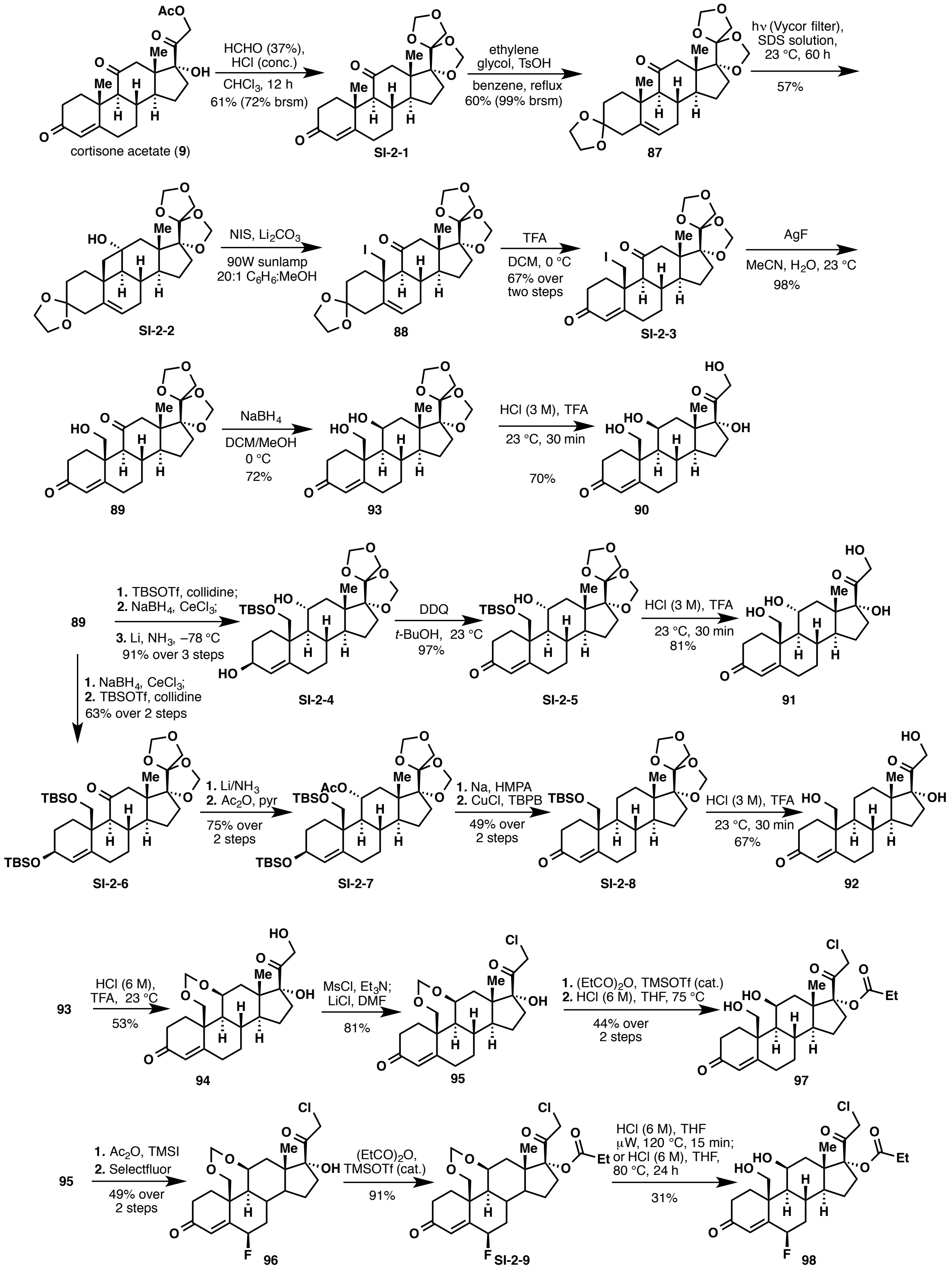
HRMS (*m/z*): calcd for $C_{26}H_{41}BO_8$, $[M+H]^+$, 493.2973; found, 493.2977;

IR (film) ν_{max}: 3485, 2930, 1738, 1459, 1378, 1334, 1280, 1226, 1206, 1148, 1098, 1057, 1031;

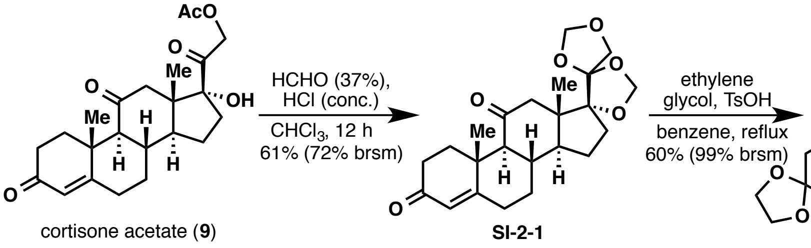
^{1}H NMR (600 MHz, CDCl$_3$): δ 4.81 (dd, *J* = 4.8, 2.2 Hz, 1 H), 4.62 (s, 2H), 4.33 (dd, *J* = 12.2, 1.4 Hz, 1 H), 4.28 (t, *J* = 3.0 Hz, 1 H), 4.04 (td, *J* = 7.9, 4.1 Hz, 1 H), 3.68 (d, *J* = 12.2 Hz, 1 H), 3.29 (s, 3 H), 2.53–2.36 (m, 2 H), 2.32–2.12 (m, 3 H), 1.98–1.87 (m, 2 H), 1.86–1.77 (m, 2 H), 1.74–1.62 (m, 2 H), 1.61–1.46 (m, 2 H), 1.32 (s, 3 H), 1.26 (s, 3 H), 1.08 (s, 3 H), 0.90 (t, *J* = 7.8 Hz, 3 H), 0.69 (q, *J* = 8.2 Hz, 2 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 219.8, 101.5, 96.9, 80.8, 74.2, 72.2, 66.5, 65.2, 60.0, 56.1, 52.6, 48.9, 45.7, 41.0, 38.3, 36.9, 35.1, 33.6, 33.1, 28.2, 24.4, 23.2, 20.9, 15.8, 7.9.

Scheme S2

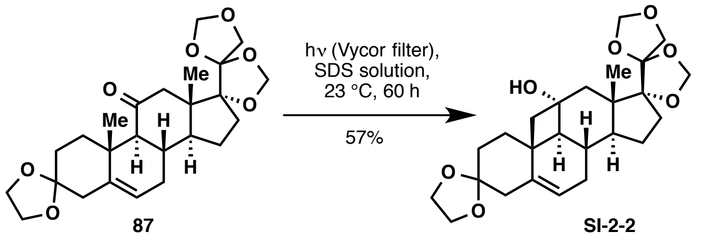

cortisone acetate (9)
HCHO (37%), HCl (conc.)
CHCl3, 12 h
61% (72% brsm)
SI-2-1
ethylene glycol, TsOH
benzene, reflux
60% (99% brsm)
87
hν (Vycor filter), SDS solution, 23 °C, 60 h
57%
SI-2-2
NIS, Li2CO3
90W sunlamp
20:1 C6H6:MeOH
88
TFA
DCM, 0 °C
67% over two steps
SI-2-3
AgF
MeCN, H2O, 23 °C
98%
89
NaBH4
DCM/MeOH
0 °C
72%
93
HCl (3 M), TFA
23 °C, 30 min
70%
90
89
1. TBSOTf, collidine;
2. NaBH4, CeCl3;
3. Li, NH3, –78 °C
91% over 3 steps
SI-2-4
DDQ
t-BuOH, 23 °C
97%
SI-2-5
HCl (3 M), TFA
23 °C, 30 min
81%
91
1. NaBH4, CeCl3;
2. TBSOTf, collidine
63% over 2 steps
SI-2-6
1. Li/NH3
2. Ac2O, pyr
75% over 2 steps
SI-2-7
1. Na, HMPA
2. CuCl, TBPB
49% over 2 steps
SI-2-8
HCl (3 M), TFA
23 °C, 30 min
67%
92
93
HCl (6 M), TFA, 23 °C
53%
94
MsCl, Et3N; LiCl, DMF
81%
95
1. (EtCO)2O, TMSOTf (cat.)
2. HCl (6 M), THF, 75 °C
44% over 2 steps
97
95
1. Ac2O, TMSI
2. Selectfluor
49% over 2 steps
96
(EtCO)2O, TMSOTf (cat.)
91%
SI-2-9
HCl (6 M), THF µW, 120 °C, 15 min; or HCl (6 M), THF, 80 °C, 24 h
31%
98

Experimental Procedures Part 2



SI-2-1: Cortisone acetate (**9**; 6.00 g, 14.9 mmol) was dissolved in $CHCl_3$ (75 mL), to which formaldehyde (37% aq, 75 mL) was added, followed by concentrated HCl (37%, 75 mL). The mixture was allowed to stir at 23 ºC overnight. Upon completion, the mixture was partitioned in a separatory funnel, and the organic layer was separated, while the aqueous layer was extracted once with CH_2Cl_2 (100 mL). The combined organic layers were washed with water, sat. aq. $NaHCO_3$ and brine successively, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting oil was purified by column chromatography (1:3 EtOAc:hexanes) to give the known compound **SI-2-1** (3.651 g, 61% yield, 72% brsm).

Compound 87: To a solution of **SI-2-1** (3.6 g, 8.9 mmol, 1.0 equiv) in benzene (110 mL) was added ethylene glycol (11 mL, 201 mmol, 23.6 equiv) and *p*-TsOH·H_2O (0.35 g, 1.8 mmol, 0.2 equiv). The reaction vessel was incorporated into a standard Dean-Stark setup and immersed in an oil bath preheated to 110 ºC and stirred vigorously. After 6 h, the reaction was lifted out of the oil bath and allowed to cool. The layers were allowed to settle and the ethylene glycol was separated from the organic layer. The organic layer was neutralized with sat. aq. $NaHCO_3$ (60 mL) and the aqueous portion was extracted with EtOAc (2 x 50 mL). The organic portions were combined, washed with sat. aq. NaCl (150 mL), dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography (1:4 EtOAc:hexanes) to afford the known compound **87** (2.375 g, 60%, 99% brsm).



SI-2-2: 87 (3.00 g, 6.72 mmol) was dissolved in dry EtOH (1.0 L), transferred to a photoreactor [ACE glass, 1 L jacketed reaction vessel with quartz immersion well], and degassed with argon for 15 min, followed by irradiation using a 450 W mercury Hanovia lamp through a vycor filter for 60 h. The solution was then poured into a round bottom flask and concentrated *in vacuo*. The resulting oil was purified by column chromatography (1:4 to 2:3 EtOAc:hexanes) to give **SI-2-2** (1.71 g, 57% yield).

Physical state: white solid (m.p. 102–105 ºC).

$\mathbf{R}_f$ = 0.27 (silica gel, 2:3 EtOAc:hexanes).

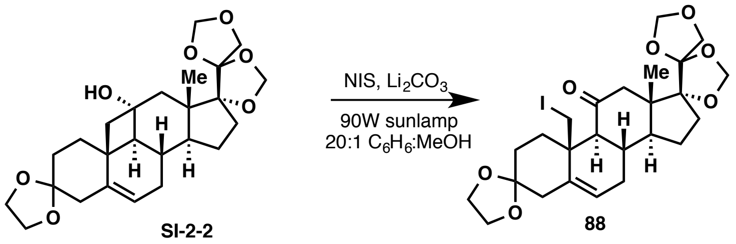
$[\alpha]^{D}_{25}$ = –51.0° (c = 0.48, $CHCl_3$).

HRMS (*m/z*): calcd for $C_{25}H_{34}O_7$, $[M+H]^+$, 447.2377; found, 447.2380.

IR (film) ν_{max}: 3439, 2941, 2881, 1707, 1438, 1324, 1240, 1215, 1180, 1100, 1081.

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.65 (d, J = 6.0 Hz, 1 H), 5.21 (s, 1 H), 5.08 (d, J = 1.1 Hz, 1 H), 5.06 (d, J = 1.1 Hz, 1 H), 5.01 (s, 1 H), 4.01–3.93 (m, 6 H), 2.87 (dt, J = 13.3, 3.4 Hz, 1 H), 2.49 (d, J = 11.7 Hz, 1 H), 2.22–2.17 (m, 2 H), 2.10 (dd, J = 11.7, 4.9 Hz, 1 H), 2.05–1.92 (m, 3 H), 1.88–1.68 (m, 9 H), 1.53–1.34 (m, 2 H), 0.97 (s, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ 141.6, 126.0, 109.9, 109.7, 95.0, 91.9, 91.8, 77.4, 70.2, 64.6, 64.5, 57.0, 50.1, 45.8, 45.5, 43.6, 42.5, 41.8, 37.5, 34.7, 32.2, 32.1, 27.6, 21.7, 15.6.



Compound 88: The solution of **SI-2-2** (0.283 g, 0.63 mmol) in toluene (12 mL) was degassed by continuous Ar bubbling for 15 min, followed by sequential addition of MeOH (0.257 mL, 6.34 mmol, 10.0 equiv), Li_2CO_3 (164 mg, 2.22 mmol, 3.5 equiv) and NIS (428 mg, 1.90 mmol, 3.0 equiv) under Ar. The resulting suspension was irradiated with sunlamp (90 W, 6 inches from the walls of the flask) for 15 min. Irradiation was then halted and the crude mixture was washed with sat. aq. $Na_2S_2O_3$ (15 mL) until colorless. The aqueous layer was back-extracted with EtOAc (15 mL) and the organic layer was washed with brine (15 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The resulting yellow oil was used for the next step without further purification. This yellow oil could also be purified by silica gel chromatography (1:3 EtOAc:hexanes) to give pure **88**.

Physical state: white foam.

R*f* = 0.65 (silica gel, 1:1 EtOAc:hexanes).

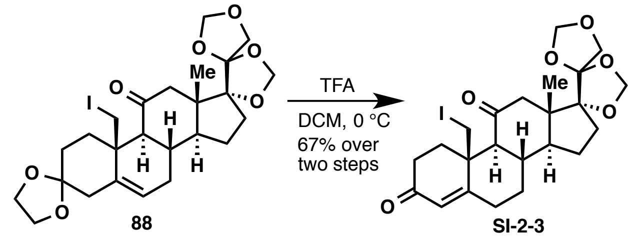
$[\alpha]^{\mathrm{D}}_{25}$ = –61.5° (*c* = 1.0, CH_2Cl_2).

HRMS (*m*/*z*): calcd for $C_{25}H_{33}IO_7$, $[M+H]^+$, 573.1344; found, 573.1317.

IR (film) $\nu_{\mathbf{max}}$: 2944, 2877, 1696, 1095, 941, 732.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65–5.58 (m, 1 H), 5.20 (s, 1 H), 5.07 (d, *J* = 1.0 Hz, 1 H), 5.05 (d, *J* = 1.0 Hz, 1 H), 5.02 (s, 1 H), 4.35 (d, *J* = 11.0 Hz, 1 H), 4.02–3.87 (m, 6 H), 3.63 (dd, *J* = 11.0, 1.3 Hz, 1 H), 2.92–2.82 (m, 1 H), 2.83 (dd, *J* = 13.5, 1.2 Hz, 1 H), 2.66 (d, *J* = 14.4 Hz, 1 H), 2.66–2.61 (m, 1 H), 2.41 (dt, *J* = 14.3, 2.7 Hz, 1 H), 2.27–2.07 (m, 3 H), 2.04 (d, *J* = 11.8 Hz, 1 H), 1.99–1.72 (m, 5 H), 1.63 (ddt, *J* = 15.2, 5.6, 3.4 Hz, 1 H), 1.52–1.32 (m, 2 H), 0.95 (s, 3 H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 212.2, 137.9, 124.0, 109.7, 108.5, 95.2, 91.9, 91.1, 70.0, 64.6, 64.5, 60.6, 51.5, 51.0, 48.9, 41.6, 39.6, 35.7, 32.7, 32.1, 31.9, 31.1, 23.6, 14.8, 10.1.



SI-2-3: Crude **88** (0.63 mmol) from the previous step was dissolved in CH_2Cl_2 (1.0 mL), and the solution was cooled to 0 ºC, followed by addition of TFA (0.2 mL) and H_2O (0.1 mL). The mixture was stirred at the same temperature for 2 h, after which the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting oil was purified by column chromatography (1:2 to 1:1 EtOAc:hexanes) to give **SI-2-3** (223 mg, 67% yield over 2 steps).

Physical state: white foam.

R*f* = 0.45 (silica gel, 1:1 EtOAc:hexanes).

$[\alpha]^{\mathrm{D}}_{25}$ = +31.7° (*c* = 0.30, CH_2Cl_2).

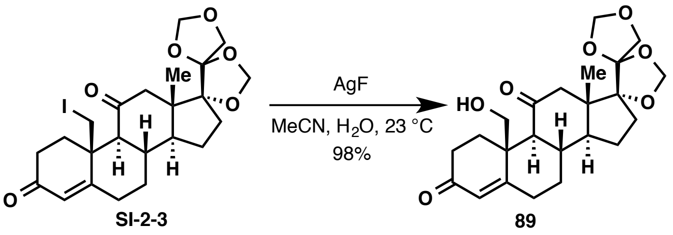
HRMS (*m*/*z*): calcd for $C_{23}H_{30}IO_6$, $[M+H]^+$, 529.1082; found, 529.1082.

IR (film) $\nu_{\mathbf{max}}$: 2938, 2876, 1702, 1670, 1275, 1098, 944, 750.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96 (s, 1 H), 5.20 (s, 1 H), 5.07 (d, *J* = 1.0 Hz, 1 H), 5.04 (d, *J* = 1.0 Hz, 1 H), 5.00 (s, 1 H), 4.16 (d, *J* = 10.4 Hz, 1 H), 4.01–3.90 (m, 2 H), 3.52 (d, *J* = 10.4 Hz, 1 H), 2.87 (d, *J* =

12.9 Hz, 1 H), 2.74 (ddd, *J* = 16.7, 9.0, 5.4 Hz, 1 H), 2.65–2.57 (m, 1 H), 2.57 (d, *J* = 12.8 Hz, 1 H), 2.44 (dd, *J* = 11.6, 1.0 Hz, 1 H), 2.39–2.22 (m, 4 H), 2.15 (ddd, *J* = 14.5, 9.0, 5.4 Hz, 1 H), 2.06 (dt, *J* = 11.9, 3.8 Hz, 1H), 2.00–1.75 (m, 4 H), 1.42 (ddd, *J* = 17.5, 11.9, 6.1 Hz, 1 H), 1.34–1.19 (m, 1H), 0.81 (d, *J* = 0.9 Hz, 3 H).

^{13}C NMR (151 MHz, CDCl$_3$): δ 210.5, 198.9, 165.4, 127.1, 109.5, 95.1, 91.9, 90.56, 70.0, 61.7, 50.8, 50.6, 49.9, 41.7, 36.7, 34.3, 33.4, 32.8, 32.1, 31.9, 23.1, 13.8, 12.2.



Compound 89: **SI-2-3** (140 mg, 0.265 mmol, 1.0 equiv) was dissolved in MeCN (6 mL), followed by sequential addition of H_2O (0.6 mL) and AgF (127 mg, 1.0 mmol, 3.8 equiv). The resulting mixture was stirred at room temperature overnight. Upon completion, the reaction mixture was diluted with EtOAc (10 mL), filtered through a pad of Celite® and concentrated *in vacuo*. The resulting yellow solid was purified by silica gel chromatography (40:1 CH_2Cl_2:MeOH) to give enone **89** (109 mg, 98%).

Physical state: white solid (m.p. 174 ºC).

R$_f$ = 0.21 (silica gel, 3:2 EtOAc:hexanes).

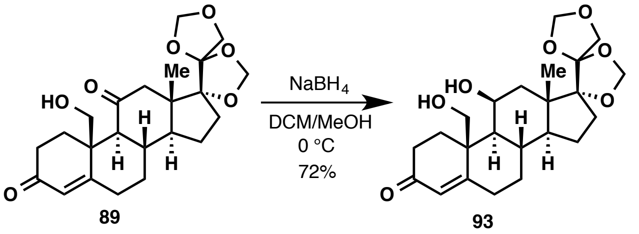
$[\alpha]^{D}_{25}$ = +35.7° (*c* = 0.83, CHCl$_3$).

HRMS (*m/z*): calcd for $C_{23}H_{30}O_7$, $[M+H]^+$, 419.2064; found, 419.2062.

IR (film) ν_{max}: 3422, 2940, 2877, 1701, 1661, 1455, 1436, 1347, 1219, 1097, 1033, 942.

^{1}H NMR (400 MHz, CDCl$_3$): δ 5.88–5.73 (m, 1 H), 5.21 (s, 1 H), 5.07 (dd, *J* = 9.6, 1.0 Hz, 2 H), 5.01 (s, 1 H), 4.17 (d, *J* = 11.7 Hz, 1 H), 4.02–3.93 (dd, *J* = 13.9, 9.5 Hz, 2 H), 3.75 (d, *J* = 11.6 Hz, 1 H), 2.96 (d, *J* = 12.5 Hz, 1 H), 2.82 (ddd, *J* = 13.6, 4.9, 3.6 Hz, 1 H), 2.70–2.60 (m, 1 H), 2.64 (d, *J* = 12.5 Hz, 1 H), 2.39–2.22 (m, 5 H), 2.05–1.78 (m, 5 H), 1.66–1.55 (m, 2 H), 1.49–1.24 (m, 2 H), 0.84 (s, 3 H).

^{13}C NMR (151 MHz, CDCl$_3$): δ 215.1, 199.7, 165.4, 125.6, 109.6, 95.1, 92.0, 90.6, 70.0, 64.4, 64.2, 51.1, 50.8, 50.3, 43.4, 37.3, 34.4, 33.0, 32.2, 32.2, 31.4, 23.1, 13.7.



Compound 93: To a solution of alcohol **89** (666 mg, 1.59 mmol, 1.0 equiv) in 1:1 CH_2Cl_2:EtOH (15 mL) at 0 °C was added $NaBH_4$ (19 mg, 0.5 mmol, 0.3 equiv). Two more portions of $NaBH_4$ (19 mg each, 0.5 mmol, 0.3 equiv) were added in 40 min intervals. Upon completion of the reaction as judged by TLC analysis (approximately 2 h), any excess reducing agent was quenched by addition of 0.1 mL of wet acetone. The reaction mixture was diluted with EtOAc (50 mL) and washed sequentially with H_2O (25 mL), and brine (25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude mixture was purified by column chromatography (1:3 to 1:1 EtOAc:hexanes) to afford **93** (480 mg, 72%).

Physical state: white foam.

R$_f$ = 0.40 (silica gel, 2:1 EtOAc:hexanes).

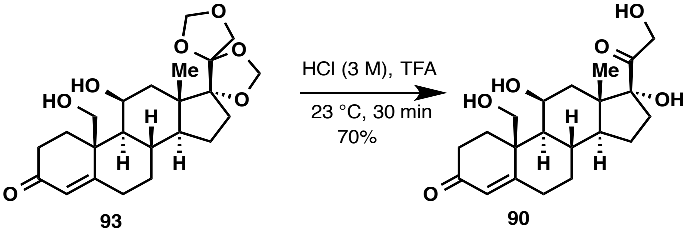
$[\alpha]^{D}_{25}$ = +6.4° (*c* = 0.58, $CHCl_3$).

HRMS (*m/z*): calcd for $C_{23}H_{33}O_7$, $[M+H]^+$, 421.2221; found, 421.2219.

IR (film) ν_{max}: 2929, 2875, 1707, 1658, 1359, 1222, 1084, 941.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.76 (s, 1 H), 5.21 (s, 1 H), 5.03 (s, 1 H), 5.03 (dd, *J* = 2.7, 1.0 Hz, 2 H), 4.42 (q, *J* = 3.0 Hz, 1 H), 4.12 (d, *J* = 11.9 Hz, 1 H), 4.04–3.96 (m, 2 H), 3.56 (d, *J* = 11.8 Hz, 1 H), 2.59 (dt, *J* = 13.2, 4.5 Hz, 1H), 2.49 (ddd, *J* = 16.9, 13.7, 4.8 Hz, 1 H), 2.34 (dt, *J* = 17.0, 4.2 Hz, 1 H), 2.29 (dtd, *J* = 11.0, 5.2, 3.2 Hz, 2 H), 2.16 (dd, *J* = 15.1, 3.2 Hz, 1 H), 2.14–2.05 (m, 2 H), 2.04–1.98 (m, 1 H), 1.87–1.80 (m, 1 H), 1.80–1.60 (m, 4 H), 1.43 (tdd, *J* = 12.3, 10.5, 6.9 Hz, 1 H), 1.19 (dd, *J* = 11.3, 2.8 Hz, 1 H), 1.15–1.10 (m, 1 H), 1.13 (s, 3 H).

^{13}C NMR (151 MHz, CDCl$_3$): δ 199.5, 169.3, 123.7, 110.0, 95.0, 91.6 (2C), 70.4, 67.9, 63.8, 56.6, 53.2, 45.8, 44.3, 39.9, 34.0, 33.1, 32.2, 31.5, 31.1, 29.9, 23.7, 15.7.



Compound 90: **93** (2.2 mg, 5.3 μmol, 1.0 equiv) was dissolved in TFA (0.1 mL), followed by the addition of 3 M HCl (0.1 mL) solution at room temperature. After 30 min, the mixture was cooled to 0 ºC, then diluted with CH_2Cl_2 (5 mL), and quenched by slow addition of 10% NH_3 solution until neutral (pH = 7). The layers were separated, and the aqueous layer was saturated with solid NaCl, and further extracted by $CHCl_3$/MeOH (10:1, 5 mL) three times. The combined organic phases were dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified by preparative thin layer chromatography (PTLC) on silica gel (1:15 MeOH:CH_2Cl_2) to afford **90** (1.4 mg, 70%).

Physical state: white foam.

$\boldsymbol{R_f}$ = 0.20 (silica gel, 15:1 CH_2Cl_2:MeOH).

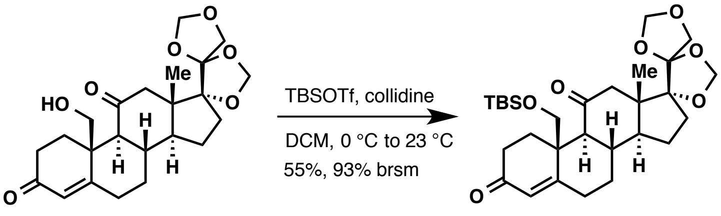
$[\boldsymbol{\alpha}]^{D}_{25}$ = +70.0° (*c* = 0.14, $CHCl_3$).

HRMS (*m*/*z*): calcd for $C_{21}H_{31}O_6$, $[M+H]^+$, 379.2115; found, 379.2118.

IR (film) ν_{max}: 3347, 2924, 2359, 2340, 1710, 1651, 1446, 1050, 733.

^{1}H NMR (600 MHz, CD_3OD): δ 5.78 (d, *J* = 1.6 Hz, 1 H), 4.63 (d, *J* = 19.1 Hz, 1 H), 4.36 (q, *J* = 2.9 Hz, 1 H), 4.26 (d, *J* = 19.1 Hz, 1 H), 4.15 (d, *J* = 11.8 Hz, 1 H), 3.63 (d, *J* = 11.8 Hz, 1 H), 2.73 (ddd, *J* = 13.9, 11.2, 2.5 Hz, 1 H), 2.57–2.48 (m, 2 H), 2.46–2.38 (m, 1 H), 2.35–2.28 (m, 2 H), 2.17–2.11 (m, 1 H), 2.11–2.04 (m, 2 H), 1.84–1.71 (m, 3 H), 1.69 (dd, *J* = 13.8, 2.8 Hz, 1 H), 1.48 (ddd, *J* = 14.7, 8.6, 6.2 Hz, 1 H), 1.44–1.36 (m, 1 H), 1.21 (dd, *J* = 11.3, 2.8 Hz, 1 H), 1.19–1.11 (m, 1 H), 0.89 (s, 3 H).

^{13}C NMR (151 MHz, CD_3OD): δ 212.8, 202.3, 172.9, 124.4, 90.1, 67.8, 67.6, 64.2, 58.3, 53.7, 49.6, 45.8, 39.4, 34.7, 34.5, 34.2, 34.0, 32.6, 30.9, 24.5, 18.0.



89

SI-2-3a

SI-2-3a: To a stirred solution of **89** (20 mg, 47.8 μmol, 1.0 equiv) and 2,4,6-collidine (12 μL, 96.0 μmol, 2.0 equiv) in CH_2Cl_2 (0.5 mL) was added TBSOTf (12 μL, 52.8 μmol, 1.1 equiv) dropwise at 0 ºC. After 5 min, the cold bath was removed and the reaction was allowed to run at ambient temperature for 2 h, and then quenched with saturated $NaHCO_3$ solution (4 mL). The mixture was extracted with CH_2Cl_2 (2 × 4 mL), and the combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (1:2 EtOAc:hexanes) to afford **SI-2-3a** (14 mg, 55%, 93% brsm).

Physical state: white foam;

R R_f = 0.60 (silica gel, 1:1 EtOAc:hexanes).

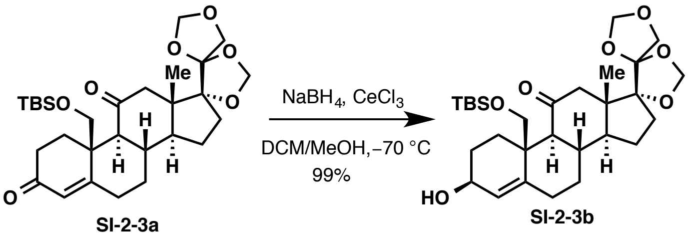
$[\alpha]^{\mathrm{D}}_{25}$ = +75.0° (c = 0.22, $CHCl_3$).

HRMS (*m/z*): calcd for $C_{29}H_{45}O_7Si$, $[M+H]^+$, 533.2929; found, 533.2933.

IR (film) ν_{max}: 3727, 3626, 2923, 1701, 1670, 1080, 670.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.88 (s, 1 H), 5.19 (s, 1 H), 5.07 (d, J = 1.0 Hz, 1 H), 5.05 (d, J = 1.0 Hz, 1 H), 5.00 (s, 1 H), 4.28 (d, J = 9.7 Hz, 1 H), 4.16 (dd, J = 9.7, 1.2 Hz, 1 H), 3.96 (q, J = 9.2 Hz, 2 H), 2.85 (d, J = 13.2 Hz, 1 H), 2.77 (ddd, J = 13.8, 5.6, 3.4 Hz, 1 H), 2.65 (ddd, J = 17.1, 13.9, 5.6 Hz, 1 H), 2.56 (d, J = 13.0 Hz, 1 H), 2.55–2.46 (m, 1 H), 2.34 (ddd, J = 14.3, 4.1, 2.7 Hz, 1 H), 2.29–2.18 (m, 2 H), 2.12–2.02 (m, 2 H), 2.02–1.90 (m, 2 H), 1.88 (ddd, J = 15.3, 9.5, 5.8 Hz, 1 H), 1.80 (ddd, J = 14.7, 11.4, 3.1 Hz, 1 H), 1.74–1.65 (m, 1 H), 1.41 (qd, J = 11.7, 5.7 Hz, 1 H), 0.95–0.83 (m, 1 H), 0.82 (s, 9 H), 0.04 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 211.0, 200.4, 166.2, 126.8, 109.6, 95.1, 91.9, 90.8, 70.0, 65.7, 63.0, 51.1, 50.8, 49.6, 43.6, 37. 1, 34.9, 33.9, 33.6, 32.4, 32.1, 25.9, 23.2, 18.2, 14.0, –5.5, –5.6.



SI-2-3b: To a stirred solution of **SI-2-3a** (14.0 mg, 26 μmol, 1.0 equiv) in MeOH/CH_2Cl_2 (1.5:1, 1.2 mL) at –70 ºC was added $CeCl_3{\cdot}7H_2O$ (19.0 mg, 052 μmol, 2.0 equiv) followed by $NaBH_4$ (1.0 mg, 26 μmol, 1.0 equiv) solution in EtOH (0.1 mL). The reaction mixture was warmed to 0 ºC and maintained at this temperature for 5 min before being quenched with saturated NH_4Cl solution (2 mL). The resulting mixture was extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried with Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (1:3 EtOAc:hexanes) to afford **SI-2-3b** (14 mg, 99%).

Physical state: white foam.

R_f = 0.35 (silica gel, 1:2 EtOAc:hexanes).

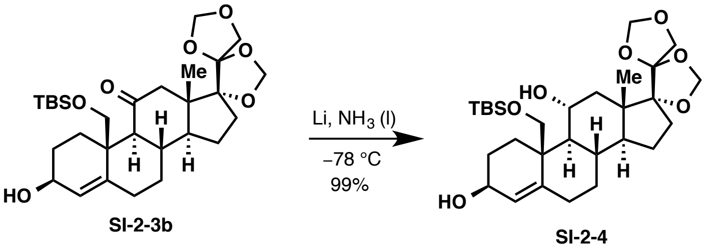
$[\alpha]^{D}_{25}$ = +6.5° (c = 0.48, CH_2Cl_2);

HRMS (*m/z*): calcd for $C_{29}H_{46}O_7Si$, $[M+Na]^+$, 557.2905; found, 557.2920.

IR (film) ν_{max}: 2925, 2854, 1702, 1462, 1256, 1084, 836, 737.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.19 (s, 1 H), 5.06 (d, J = 1.0 Hz, 1 H), 5.04 (d, J = 1.0 Hz, 1 H), 5.00 (s, 1 H), 4.08 (d, J = 9.5 Hz, 1 H), 4.07–4.04 (m, 1 H), 4.02 (d, J = 9.5 Hz, 1 H), 3.99–3.92 (m, 2 H), 2.81 (d, J = 12.9 Hz, 1 H), 2.50 (d, J = 12.9 Hz, 1 H), 2.38 (ddd, J = 14.6, 7.5, 3.7 Hz, 1 H), 2.36–2.29 (m, 1 H), 2.19 (td, J = 11.3, 7.1 Hz, 1 H), 2.07 (ddd, J = 13.5, 4.2, 2.5 Hz, 1 H), 2.03–1.96 (m, 2 H), 1.95–1.81 (m, 3 H), 1.81–1.70 (m, 2 H), 1.70–1.61 (m, 1 H), 1.42–1.32 (m, 2 H), 1.18–1.07 (m, 1 H), 0.87 (s, 9 H), 0.80 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H),

^{13}C NMR (151 MHz, CDCl$_3$): δ 211.8, 143.7, 126.8, 109.6, 95.1, 91.9, 90.8, 70.0, 66.5, 65.9, 62.8, 51.4, 50.8, 49.7, 42.2, 37.0, 33.7, 32.5, 32.1, 30.5, 29.5, 26.1, 23.2, 18.4, 14.0, –5.3, –5.4.



SI-2-4: A Schlenk tube equipped with a dry ice condenser was charged with liquid NH_3 (ca. 6 mL), and then Li metal (34 mg, 4.9 mmol, 187.0 equiv) was added under Ar atmosphere. The blue solution was stirred at –78 ºC for 30 min, and then a solution of **SI-2-3b** (14 mg, 26.2 μmol, 1.0 equiv) in THF (0.5 mL) was added. The reaction mixture was stirred at –78 ºC for 1 h, and then quenched with solid NH_4Cl (50 mg). The resulting mixture was allowed to warm to room temperature for the evaporation of liquid NH_3. The resulting mixture was partitioned between EtOAc and water, and the organic phase was separated, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (2:1 hexanes:EtOAc) to afford **SI-2-4** (13.9 mg, 99%).

Physical state: colorless oil.

R_f = 0.60 (silica gel, 1:1 EtOAc:hexanes).

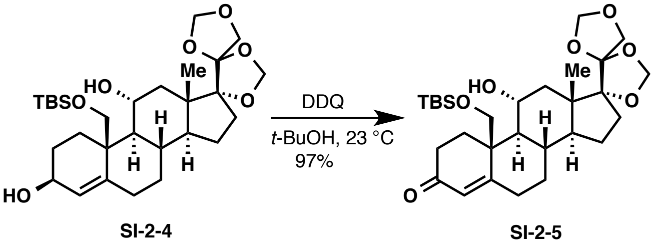
$[\alpha]^{D}_{25}$ = –9.0° (c = 0.31, $CHCl_3$).

HRMS (*m/z*): calcd for $C_{29}H_{48}O_7Si$, $[M+Na]^+$, 559.3062; found, 559.3071.

IR (film) ν_{max}: 2927, 2855, 2360, 1468, 1256, 1085, 943, 837, 754.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.43 (s, 1 H), 5.22 (s, 1 H), 5.04 (d, J = 1.0 Hz, 1 H), 5.03 (d, J = 1.0 Hz, 1 H), 5.02 (s, 1 H), 4.21–4.12 (m, 2 H), 4.00 (d, J = 10.2 Hz, 1 H), 4.00–3.94 (m, 2 H), 3.71 (dd, J = 10.2, 1.0 Hz, 1 H), 2.56 (ddd, *J* = 13.5, 5.3, 2.2 Hz, 1 H), 2.08 (dd, *J* = 12.4, 4.3 Hz, 1 H), 2.07–2.00 (m, 2 H), 1.92–1.87 (m, 1 H), 1.83 (t, *J* = 12.0 Hz, 1 H), 1.80–1.69 (m, 3 H), 1.59–1.38 (m, 3 H), 1.33–1.23 (m, 3 H), 1.06 (t, *J* = 10.4 Hz, 1 H), 1.04–0.93 (m, 1 H), 0.92 (s, 9 H), 0.90 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H).

^{13}C NMR (151 MHz, CDCl$_3$): δ 144.3, 126.9, 110.0, 95.1, 91.7, 91.4, 70.5, 70.4, 67.5, 65.6, 60.1, 51.6, 47.0, 43.5, 41.2, 35.2, 33.9, 32.4, 32.3, 32.2, 29.2, 26.1, 23.6, 18.4, 14.5, –5.4, –5.5.



SI-2-5: To a stirred solution of **SI-2-4** (9.2 mg, 171 μmol, 1.0 equiv) in dry *t*-butanol (0.2 mL) was added DDQ (4.8 mg, 21.0 μmol, 1.2 equiv). The mixture was stirred at ambient temperature for 1 h, and then quenched with saturated NaHCO$_3$ solution (3 mL). The mixture was extracted with EtOAc (2 x 3 mL), and the combined organic phases were washed with 10% NaOH aqueous solution (2 x 3 mL) and brine (5 mL), dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (1:2 EtOAc:hexanes) to afford **SI-2-5** (8.9 mg, 97%).

Physical state: colorless oil;

R$_f$ = 0.65 (silica gel, 1:1 EtOAc:hexanes).

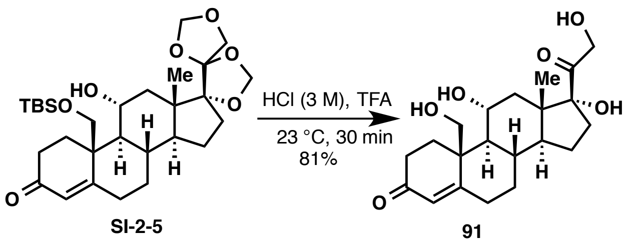
$[\alpha]^{D}_{25}$ = +22.1° (*c* = 0.56, CHCl$_3$).

HRMS (*m/z*): calcd for $C_{29}H_{47}O_7Si$, $[M+H]^+$, 535.3086; found, 535.3100.

IR (film) ν_{max}: 2930, 1662, 1087, 944, 838, 671.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.82 (brs, 1 H), 5.22 (s, 1 H), 5.04 (s, 2 H), 5.03 (s, 1 H), 4.14 (td, *J* = 10.9, 4.5 Hz, 1 H), 4.01 (d, *J* = 9.9 Hz, 1 H), 4.00–3.96 (m, 2 H), 3.94 (d, *J* = 10.0 Hz, 1 H), 2.91 (ddd, *J* = 14.2, 5.1, 3.7 Hz, 1 H), 2.46 (ddd, *J* = 17.6, 14.0, 5.0 Hz, 1 H), 2.41–2.26 (m, 3 H), 2.16 (dd, *J* = 12.4, 4.5 Hz, 1 H), 1.93 (td, *J* = 14.1, 4.8 Hz, 1 H), 1.89–1.80 (m, 2 H), 1.80–1.73 (m, 3 H), 1.70 (ddt, *J* = 20.2, 12.4, 6.2 Hz, 1 H), 1.37–1.23 (m, 2 H), 1.20 (t, *J* = 10.4 Hz, 1 H), 1.10 (qd, *J* = 12.8, 4.2 Hz, 1 H), 0.92 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.08 (s, 3 H).

^{13}C NMR (151 MHz, CDCl$_3$): δ 200.1, 168.8, 126.3, 109.9, 95.0, 91.8, 91.3, 70.3, 69.8, 66.2, 59.3, 51.4, 47.03, 44.7, 42.2, 35.4, 35.2, 34.7, 34.6, 32.1, 30.9, 26.0, 23.6, 18.3, 14.3, –5.5, –5.5.



Compound 91: **SI-2-5** (4.0 mg, 7.5 μmol, 1.0 equiv) was dissolved in TFA (0.1 mL), followed by the addition of 3 M HCl solution (0.1 mL) at room temperature. After 30 min, the mixture was cooled to 0 °C, then diluted with CH_2Cl_2 (5 mL), and quenched by slow addition of 10% NH_3 aqueous solution until neutral (pH = 7). The layers were separated, and the aqueous layer was saturated with solid NaCl, and further extracted by $CHCl_3$/MeOH (10:1, 5 mL) three times. The combined organic phases was dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified by preparative thin layer chromatography (PTLC) on silica gel (1:10 MeOH:CH_2Cl_2) to afford **91** (2.3 mg, 81%).

Physical state: white foam;

$\boldsymbol{R_f}$ = 0.20 (silica gel, 1:10 MeOH:CH_2Cl_2).

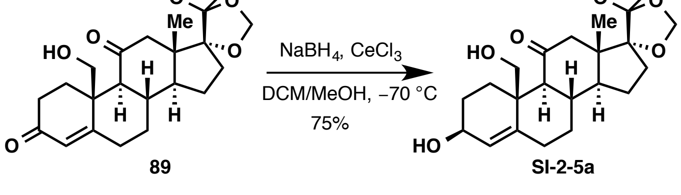
$[\alpha]^{D}_{25}$ = +60.0° (c = 0.14, MeOH).

HRMS (*m/z*): calcd for $C_{21}H_{31}O_6$, $[M+H]^+$, 379.2115; found, 379.2121.

IR (film) ν_{max}: 3728, 3356, 2924, 1650, 1044, 671.

^{1}H NMR (600 MHz, CD_3OD): δ 5.87 (d, J = 1.6 Hz, 1 H), 4.64 (d, J = 19.3 Hz, 1 H), 4.59 (s, 1 H), 4.29 (d, J = 19.3 Hz, 1 H), 4.06 (d, J = 10.9 Hz, 1 H), 3.99 (d, J = 10.9 Hz, 1 H), 2.91 (dt, J = 14.2, 5.0 Hz, 1 H), 2.70 (ddd, J = 14.7, 11.5, 3.1 Hz, 1 H), 2.64 (ddd, J = 17.7, 12.9, 5.2 Hz, 1 H), 2.58–2.50 (m, 1 H), 2.36 (dt, J = 13.9, 3.3 Hz, 1 H), 2.27 (dt, J = 17.3, 4.8 Hz, 1 H), 2.14–2.06 (m, 1 H), 1.96–1.84 (m, 3 H), 1.79 (qd, J = 11.4, 3.7 Hz, 1 H), 1.73 (dddd, J = 12.3, 9.9, 7.3, 3.1 Hz, 1 H), 1.67 (dd, J = 12.0, 4.7 Hz, 1 H), 1.53 (ddd, J = 15.1, 9.3, 6.1 Hz, 1 H), 1.33 (td, J = 12.0, 6.2 Hz, 1 H), 1.22 (t, J = 10.5 Hz, 1 H), 1.13 (qd, J = 12.6, 3.7 Hz, 1 H), 0.70 (s, 3 H).

^{13}C NMR (151 MHz, CD_3OD): δ 213.0, 203.6, 172.7, 126.9, 111.4, 89.8, 70.1, 67.8, 66.0, 59.9, 51.6, 46.5, 43.2, 36.8, 35.8, 35.7(2C), 34.9, 33.3, 24.4, 16.5.



Allylic alcohol SI-2-5a: To a stirred solution of **89** (50.0 mg, 120 μmol, 1.0 equiv) in MeOH/CH_2Cl_2 (1.5:1, 6.0 mL) at –70 ºC was added $CeCl_3 \cdot 7H_2O$ (89.0 mg, 240 μmol, 2.0 equiv) followed by $NaBH_4$ (4.5 mg, 120 μmol, 1.0 equiv) solution in EtOH (0.5 mL). The reaction mixture was warmed to 0 ºC and maintained at this temperature for 5 min before being quenched with saturated NH_4Cl solution (4 mL). The resulting mixture was extracted with EtOAc (3 x 4 mL). The combined organic extracts were dried with Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (1:1 to 4:1 EtOAc:hexanes) to afford **SI-2-5a** (37.6 mg, 75%).

Physical state: white foam.

$\mathbf{R}_f$ = 0.50 (silica gel, 2:1 EtOAc:hexanes).

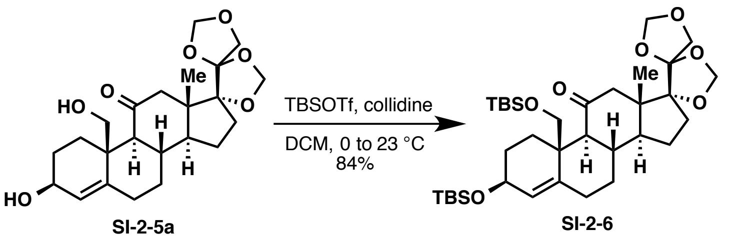
$[\alpha]^{D}_{25}$ = –20.3° (c = 1.0, CH_2Cl_2).

HRMS (*m/z*): calcd for $C_{23}H_{32}NaO_7$, $[M+Na]^+$, 443.2040; found, 443.2043.

IR (film) ν_{max}: 3388, 2929, 2875, 1696, 1085, 942, 734.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.50 (dd, J = 2.3, 1.2 Hz, 1 H), 5.19 (s, 1 H), 5.07 (d, J = 1.0 Hz, 1 H), 5.05 (d, J = 1.0 Hz, 1 H), 5.00 (s, 1 H), 4.15 (t, J = 7.5 Hz, 1 H), 4.06 (d, J = 11.6 Hz, 1 H), 3.96 (q, J = 9.3 Hz, 2 H), 3.64 (d, J = 11.6 Hz, 1 H), 2.97–2.85 (m, 1 H), 2.63–2.59 (m, 1 H), 2.58 (d, J = 12.5 Hz, 1 H), 2.27 (td, J = 11.2, 7.2 Hz, 1 H), 2.16–2.12 (m, 1 H), 2.11–2.07 (m, 2 H), 1.97–1.89 (m, 4 H), 1.87 (dd, J = 9.4, 5.8 Hz, 1 H), 1.80 (ddd, J = 14.3, 10.9, 2.5 Hz, 1 H), 1.62–1.55 (m, 1 H), 1.44–1.36 (m, 1 H), 1.21–1.12 (m, 2 H), 0.81 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 215.9, 142.6, 127.1, 109.6, 95.1, 91.9, 90.7, 70.0, 67.2, 64.8, 64.6, 51.4, 50.7, 50.2, 42.2, 37.3, 33.4, 32.1, 31.9, 29.5, 29.1, 23.1, 13.7.



SI-2-6: To a stirred solution of **SI-2-5a** (37.6 mg, 89 μmol, 1.0 equiv) and 2,4,6-collidine (59 μL, 450 μmol, 5.0 equiv) in CH_2Cl_2 (4 mL) was added TBSOTf (62 μL, 270 μmol, 3.0 equiv) dropwise at 0 ºC. After 5 min, the cold bath was removed and the reaction was allowed to run at ambient temperature for 2 h, and then quenched with saturated $NaHCO_3$ solution (4 mL). The mixture was extracted with CH_2Cl_2 (2 x 4 mL), and the combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (1:9 EtOAc:hexanes) to afford **SI-2-6** (48.5 mg, 84%).

Physical state: white solid (m.p. = 192 ºC);

R$_f$ = 0.85 (silica gel, 1:2 EtOAc:hexanes).

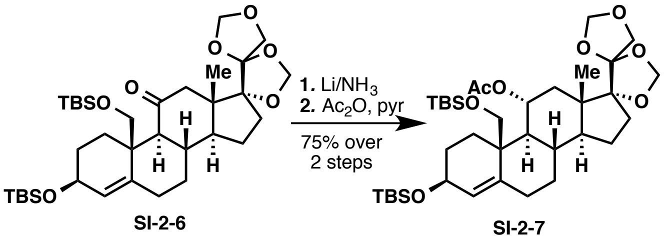
$[\alpha]_{25}^{D}$ = +8.6° (*c* = 0.85, CH_2Cl_2).

HRMS (*m/z*): calcd for $C_{35}H_{61}O_7Si_2$, $[M+H]^+$, 649.3950; found, 649.3950.

IR (film) ν_{max}: 2928, 2855, 2360, 2339, 1703, 1252, 1084, 835, 774, 670.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.39 (d, *J* = 2.2 Hz, 1 H), 5.19 (s, 1 H), 5.06 (d, *J* = 1.0 Hz, 1 H), 5.04 (t, *J* = 1.0 Hz, 1 H), 5.00 (s, 1 H), 4.18 (d, *J* = 9.6 Hz, 1 H), 4.14–4.07 (m, 1 H), 3.98 (d, *J* = 9.5 Hz, 1 H), 3.97–3.91 (m, 2 H), 2.78 (d, *J* = 13.1 Hz, 1 H), 2.50 (d, *J* = 13.1 Hz, 1 H), 2.48–2.39 (m, 2 H), 2.18–2.10 (m, 2 H), 2.04 (dt, *J* = 13.1, 3.6 Hz, 1 H), 1.94–1.81 (m, 4 H), 1.76 (ddd, *J* = 14.5, 11.3, 2.9 Hz, 1 H), 1.70–1.62 (m, 2 H), 1.42–1.31 (m, 1 H), 1.21–1.05 (m, 2 H), 0.88 (s, 9 H), 0.86 (s, 9 H), 0.81 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H), 0.00 (s, 3 H).

^{13}C NMR (151 MHz, CDCl$_3$): δ 211.8, 142.2, 128.0, 109.7, 95.1, 91.9, 90.9, 70.0, 68.4, 67.2, 64.1, 51.5, 50.9, 49.6, 41.8, 37.2, 33.7, 33.4, 32.9, 32.0, 29.9, 26.1 (2C), 23.3, 18.4, 18.3, 14.2, –4.3, –4.4, –5.4 (2C).



SI-2-7: A Schlenk tube equipped with a dry ice condenser was charged with liquid NH_3 (ca. 6 mL), and then Li metal (34 mg, 4.9 mmol, 187.0 equiv) was added under Ar atmosphere. The blue solution was stirred at –78 ºC for 30 min, and then a solution of **SI-2-6** (10.8 mg, 16.6 μmol, 1.0 equiv) in THF (0.5 mL) was added. The reaction mixture was stirred at –78 ºC for 1 h and then quenched with solid NH_4Cl (50 mg). The resultant mixture was allowed to warm to room temperature for the evaporation of liquid NH_3. The resulting mixture was partitioned between EtOAc and water (4 mL each), and the organic phase was separated, washed with brine (4 mL), dried over Na_2SO_4 and concentrated. The residue was used directly for the next step without further purification.

To a solution of the above crude product in pyridine (0.2 mL) was added acetic anhydride (0.1 mL) and catalytic amount of DMAP. The resulting mixture was allowed to stir at ambient temperature for 2 h, and then concentrated *in vacuo*. The resulting residue was purified by column chromatography (EtOAc: hexanes = 1:15) to afford **SI-2-7** (8.6 mg, 75% over two steps).

Physical state: colorless oil.

R$_f$ = 0.75 (silica gel, 1:5 EtOAc:hexanes).

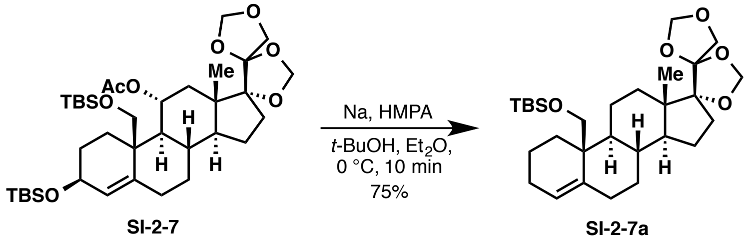
[α]$^{D}_{25}$ = –30.9° (*c* = 0.80, CHCl$_3$).

HRMS (*m/z*): calcd for $C_{37}H_{65}O_8Si_2$, [M+H]$^+$, 693.4212; found, 693.4210.

IR (film) ν_{max}: 2929, 2855, 2361, 2340, 730, 1249, 1083, 834, 773, 756, 668.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.55 (td, *J* = 10.9, 5.3 Hz, 1 H), 5.36 (s, 1 H), 5.22 (s, 1 H), 5.04 (d, *J* = 1.0 Hz, 1 H), 5.02 (d, *J* = 1.0 Hz, 1 H), 5.00 (s, 1 H), 4.20–4.13 (m, 1 H), 3.99–3.92 (m, 2 H), 3.94 (d, *J* = 10.5 Hz, 1 H), 3.71 (d, *J* = 10.4 Hz, 1 H), 2.30–2.22 (m, 2 H), 2.04–2.01 (m, 1 H), 1.98 (s, 3 H), 1.89–1.81 (m, 1 H), 1.81–1.62 (m, 8 H), 1.52–1.41 (m, 2 H), 1.35–1.22 (m, 2 H), 1.06–0.96 (m, 1 H), 0.91 (s, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 6 H), 0.05 (s, 3 H).

^{13}C NMR (151 MHz, CDCl$_3$): δ 169.7, 142.6, 128.2, 109.8, 95.1, 91.6 (2C), 72.7, 70.2, 68.4, 66.3, 56.0, 51.0, 46.4, 43.3, 38.1, 35.1, 33.4, 33.1, 31.6, 31.4, 30.0, 26.2(2C), 23.9, 22.1, 18.6, 18.5, 13.6, –4.3, –4.4, –5.3, –5.4.



SI-2-7a: To a flame-dried reaction tube equipped with a stir bar was added freshly distilled HMPA (0.4 mL) and dry Et$_2$O (0.2 mL). This solution was then degassed by continuous argon bubbling for 15 min. Freshly sliced sodium metal (washed with degassed hexanes then degassed Et$_2$O; 7.0 mg, 300 μmol, 24.2 equiv) was then added, and the reaction mixture was degassed for 10 min with a stream of argon, at which point the solution became dark blue. A degassed solution of **SI-2-7** (8.6 mg, 12.4 μmol, 1.0 equiv) in 1:1 *t*-BuOH/Et$_2$O (0.3 mL) was then prepared, and was added slowly to the blue reaction mixture over the course of 10 min at 0 ºC, being careful not to decolorize the blue solution. After the addition was complete and the reaction mixture regained its blue color, the tube was opened to air and the reaction mixture was transferred via Pasteur pipet to a cooled (0 ºC), vigorously stirred 20 mL Erlenmeyer flask containing saturated aqueous NH$_4$Cl solution (5 mL). The remaining sodium metal should NOT be transferred. The reaction flask was rinsed with Et$_2$O (2 x 3 mL) into the Erlenmeyer flask. This mixture was then warmed to room temperature while vigorously stirring over 30 min. The resulting layers were then separated, and the aqueous layer was extracted with 10 mL Et_2O. The organic layers were combined, washed with H_2O (15 mL) and brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by column chromatography (1:12 EtOAc:hexanes) to give **SI-2-7a** (8.6 mg, 75%).

Physical state: colorless oil.

R$_f$ = 0.85 (silica gel, 1:5 EtOAc:hexanes).

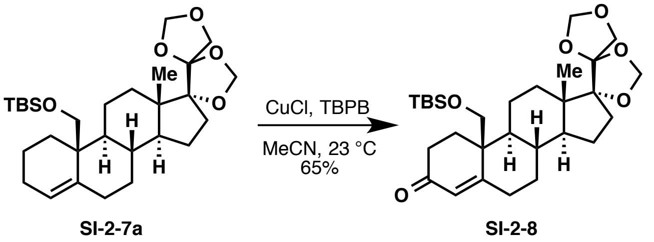
$[\alpha]^{D}_{25}$ = –27.0° (*c* = 0.37, $CHCl_3$).

HRMS (*m/z*): calcd for $C_{29}H_{49}O_5Si$, $[M+H]^+$, 505.3344; found, 505.3368.

IR (film) ν_{max}: 2925, 2855, 2360, 1461, 1254, 1088, 944, 837, 774.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.39 (d, *J* = 1.9 Hz, 1 H), 5.20 (s, 1 H), 5.06 (d, *J* = 1.0 Hz, 1 H), 5.04 (s, 1 H), 5.03 (d, *J* = 1.0 Hz, 1 H), 4.02–3.95 (m, 2 H), 3.78 (d, *J* = 9.9 Hz, 1 H), 3.68 (d, *J* = 10.0 Hz, 1 H), 2.24–2.14 (m, 1 H), 2.08 (ddd, *J* = 13.1, 4.9, 3.1 Hz, 1 H), 1.98 (ddd, *J* = 13.6, 4.3, 2.3 Hz, 1 H), 1.94–1.88 (m, 2 H), 1.83–1.51 (m, 13 H), 1.34–1.26 (m, 3 H), 1.18–1.09 (m, 1 H), 0.88 (s, 9 H), 0.85 (s, 3 H), 0.03 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (151 MHz, CDCl$_3$): δ 142.2, 121.1, 95.0, 92.1, 91.6, 70.4, 66.4, 54.1, 52.2, 46.7, 42.0, 36.3, 33.5, 33.4, 32.9, 31.7, 31.6, 30.5, 26.0, 25.7, 23.9, 21.6, 19.5, 18.3, 13.1, –5.4, –5.5.



SI-2-8: To a stirred solution of the **SI-2-7a** (4.8 mg, 9.5 μmol, 1.0 equiv) and DBU (2 μL, 14 μmol, 1.5 equiv) in acetonitrile (0.15 mL) was added CuCl (1 mg, 10 μmol, 1.1 equiv) and *tert*-butyl peroxybenzoate (TBPB) (13 μL, 67 μmol, 7.0 equiv) successively. After 24 h, the reaction was diluted with EtOAc (5 mL), and washed with saturated NH_4Cl solution (2 x 5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by preparative thin layer chromatography (PTLC) on silica gel (1:5 EtOAc:hexanes) to get **SI-2-8** (3.2 mg, 65% yield).

Physical state: colorless oil.

R$_f$ = 0.70 (silica gel, 1:3 EtOAc:hexanes).

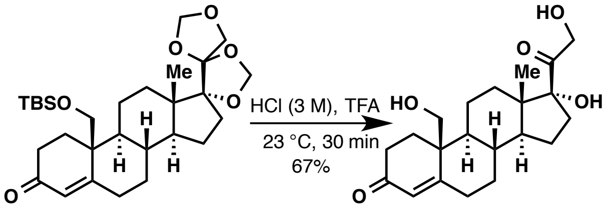
$[\alpha]^{D}_{25}$ = +17.7° (c = 0.13, $CHCl_3$).

HRMS (*m/z*): calcd for $C_{29}H_{47}O_6Si$, $[M+H]^+$, 519.3136; found, 519.3136.

IR (film) ν_{max}: 2927, 2855, 2361, 2340, 1672, 1257, 1098, 839, 670.

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.86 (d, J = 1.8 Hz, 1 H), 5.20 (s, 1 H), 5.06 (d, J = 0.9 Hz, 1 H), 5.04 (s, 1 H), 5.04 (d, J = 0.9 Hz, 1 H), 3.99 (q, J = 9.1 Hz, 2 H), 3.91 (d, J = 9.8 Hz, 1 H), 3.86 (d, J = 9.9 Hz, 1 H), 2.61 (ddd, J = 17.0, 14.3, 4.9 Hz, 1 H), 2.46–2.37 (m, 1 H), 2.37–2.26 (m, 3 H), 1.91–1.84 (m, 2 H), 1.84–1.44 (m, 9 H), 1.36–1.27 (m, 1 H), 1.15–1.01 (m, 2 H), 0.87 (s, 3 H), 0.85 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (151 MHz, CDCl$_3$): δ 200.3, 168.3, 126.0, 110.1, 95.0, 91.8, 91.7, 70.3, 66.1, 53.8, 51.8, 46.5, 43.7, 36.2, 35.0, 33.9, 33.5, 32.0, 31.7, 31.2, 25.9, 23.8, 21.1, 18.2, 13.0, –5.5, –5.6.



SI-2-8 92

Compound 92: **SI-2-8** (3.2 mg, 6.2 µmol, 1.0 equiv) was dissolved in TFA (0.1 mL), followed by the addition of 3 M HCl (0.1 mL) solution at room temperature. After 30 min, the mixture was cooled to 0 °C, then diluted with CH_2Cl_2 (5 mL), and quenched by slow addition of 10% NH_3 aqueous solution until neutral (pH = 7). The layers were separated, and the aqueous layer was saturated with solid NaCl, and further extracted by $CHCl_3$/MeOH (10:1, 5 mL) three times. The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified by preparative thin layer chromatography (PTLC) on silica gel (1:10 MeOH:CH_2Cl_2) to afford **92** (1.5 mg, 67%).

Physical state: white foam.

R$_f$ = 0.50 (silica gel, 10:1 CH_2Cl_2:MeOH).

$[\alpha]^{D}_{25}$ = +62.0° (c = 0.12, MeOH).

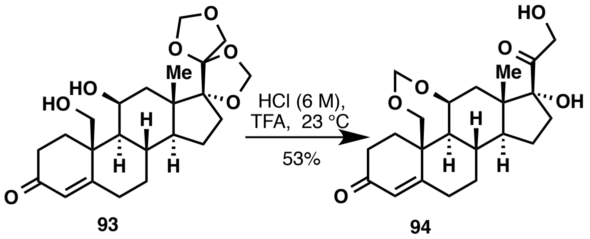
HRMS (*m/z*): calcd for $C_{21}H_{31}O_5$, $[M+H]^+$, 363.2166; found, 363.2164.

IR (film) ν_{max}: 3725, 3355, 2922, 2852, 2361, 2340, 1651, 1260, 1094, 670.

^{1}H NMR (600 MHz, CD$_3$OD): δ 5.88 (d, J = 1.7 Hz, 1 H), 4.62 (d, J = 19.2 Hz, 1 H), 4.28 (d, J = 19.2 Hz, 1 H), 4.01 (d, J = 11.2 Hz, 1 H), 3.85 (d, J = 11.2 Hz, 1 H), 2.76 (ddd, J = 17.1, 13.8, 5.6 Hz, 1 H), 2.68 (ddd, J = 14.4, 11.5, 2.6 Hz, 1 H), 2.55 (tdd, J = 14.1, 5.3, 1.9 Hz, 1 H), 2.41 (ddd, J = 13.6, 5.7, 3.4

Hz, 1 H), 2.36 (ddd, *J* = 14.3, 4.0, 2.4 Hz, 1 H), 2.28 (dt, *J* = 16.9, 4.5 Hz, 1 H), 1.96 (dt, *J* = 12.8, 2.9 Hz, 1 H), 1.86–1.70 (m, 7 H), 1.58–1.47 (m, 2 H), 1.43 (dt, *J* = 12.3, 3.4 Hz, 1 H), 1.16–1.02 (m, 2 H), 0.67 (s, 3 H).

^{13}C NMR (151 MHz, CD_3OD): δ 213.3, 203.2, 171.7, 126.7, 90.3, 67.8, 66.0, 55.3, 52.2, 45.3, 37.5, 35.8, 34.9, 34.7, 34.5, 33.7, 32.1, 24.5, 22.3, 15.4.



Compound 94: **93** (480 mg, 1.14 mmol) was dissolved in TFA (10 mL), followed by the addition of 6 M HCl (10 mL) solution at room temperature. After 30 min, the mixture was diluted with EtOAc (25 mL) and H_2O (10 mL), cooled to 0 ºC, and quenched by slow addition of solid $NaHCO_3$ (400 mg). The layers were separated, and the organic phase was further washed with sat. aq. $NaHCO_3$ (25 mL). The aqueous phase was then back-extracted with EtOAc (2 x 25 mL), and the combined organic portions were washed with brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (2:3 to 3:2 EtOAc:hexanes) to afford **94** (235 mg, 53%).

Physical state: white solid (decomp. 157 ºC).

R_f = 0.26 (silica gel, 3:2 EtOAc:hexanes).

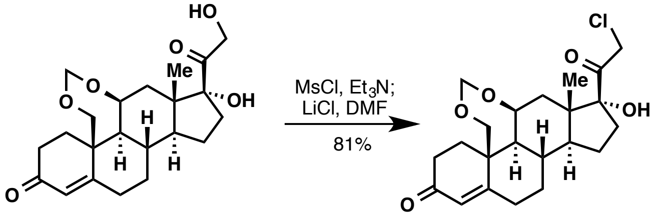
$[\alpha]^{D}_{25}$ = +99.1° (*c* = 0.57, $CHCl_3$).

HRMS (*m/z*): calcd for $C_{22}H_{30}O_6$, $[M+H]^+$, 391.2115; found, 391.2120.

IR (film) ν_{max}: 3408, 2935, 1706, 1655, 1129, 1073, 1048, 911, 729.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (s, 1 H), 4.70 (dd, *J* = 23.0, 4.1 Hz, 2 H), 4.67 (dd, *J* = 19.8, 4.6 Hz, 1 H), 4.29 (dd, *J* = 19.8, 4.3 Hz, 1 H), 4.16 (s, 1 H), 3.96 (d, *J* = 12.1 Hz, 1 H), 3.55 (d, *J* = 12.1 Hz, 1 H), 3.06 (t, *J* = 4.9 Hz, 1 H), 2.81–2.70 (m, 1H), 2.70–2.60 (m, 1 H), 2.53 (ddd, *J* = 19.2, 14.5, 4.8 Hz, 1 H), 2.44–2.30 (m, 2 H), 2.20 (t, *J* = 13.2 Hz, 1 H), 2.09–1.99 (m, 1 H), 2.03–1.76 (m, 4 H), 1.70 (dd, *J* = 13.5, 3.0 Hz, 1 H), 1.51–1.47 (m, 2 H), 1.15 (dd, *J* = 13.1, 3.4 Hz, 1 H), 1.09 (d, *J* = 10.5 Hz, 1 H), 0.93 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 212.0, 199.4, 166.6, 126.6, 92.9, 88.7, 73.7, 67.4, 64.6, 57.0, 51.6, 49.0, 43.6, 36.6, 34.5, 34.0, 33.7, 32.7, 32.2, 30.4, 23.4, 18.0.



94 **95**

Compound 95: To a solution of **94** (235 mg, 0.602 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added Et_3N (168 µL, 1.205 mmol, 2.0 equiv), MsCl (61 µL, 0.788 mmol, 1.3 equiv) and DMAP (7.4 mg, 0.0602 mmol, 0.1 equiv) at 0 ºC. After 10 min, the resulting yellow solution was warmed to room temperature and further stirred for 30 min, upon which TLC analysis showed that **94** had been fully consumed. The mixture was quenched with the addition of MeOH (100 µL) and concentrated *in vacuo*. The resulting yellow oil was then redissolved in DMF (6 mL) and LiCl (33.4 mg, 0.788 mmol, 1.3 equiv) was added. The mixture was heated at 60 ºC for 3 h, and then diluted with EtOAc (15 mL) and washed with H_2O (15 mL). The aqueous phase was extracted with EtOAc (2 x 25 mL), and the combined organic portions were washed with brine (25 mL), dried with Na_2SO_4, and concentrated in *vacuo*. The crude product was purified by column chromatography (2:3 to 1:1 EtOAc:hexanes) to afford **95** (200 mg, 81%) .

Physical state: white solid (decomp. 206 ºC).

$\boldsymbol{R_f}$ = 0.20 (silica gel, 2:3 EtOAc:hexanes).

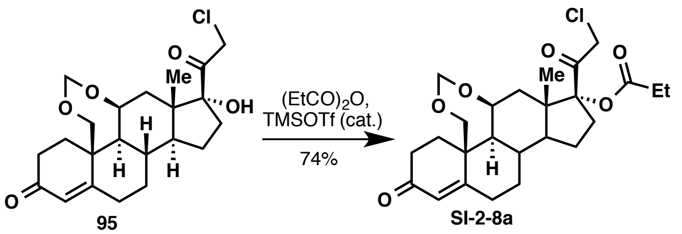
$[\alpha]^{D}_{25}$ = +138.3° (c = 0.70, $CHCl_3$).

HRMS (*m/z*): calcd for $C_{22}H_{30}ClO_5$, $[M+H]^+$, 409.1776; found, 409.1780.

IR (film) ν_{max}: 3442, 2928, 2853, 1726, 1655, 1611, 1459, 1368, 1261, 1233, 1127, 1077, 1047.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (s, 1 H), 4.73 (d, J = 4.2 Hz, 1 H), 4.68 (d, J = 4.1 Hz, 1 H), 4.62 (d, J = 16.5 Hz, 1 H), 4.28 (d, J = 16.5 Hz, 1 H), 4.16 (q, J = 2.9 Hz, 1 H), 3.96 (d, J = 12.2 Hz, 1 H), 3.55 (dd, J = 12.2, 1.5 Hz, 1 H), 2.93–2.81 (m, 1 H), 2.66 (ddd, J = 13.0, 4.9, 2.6 Hz, 1 H), 2.53 (ddd, J = 17.6, 14.6, 4.9 Hz, 1 H), 2.43–2.31 (m, 2 H), 2.20 (tdd, J = 14.4, 4.4, 2.1 Hz, 2 H), 2.08–2.00 (m, 2 H), 1.96–1.88 (m, 1 H), 1.86–1.77 (m, 2 H), 1.73 (dd, J = 13.3, 3.0 Hz, 1 H), 1.65–1.44 (m, 2 H), 1.20–1.06 (m, 2 H), 0.92 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 202.9, 199.4, 166.6, 126.6, 92.9, 90.1, 73.6, 64.6, 56.9, 51.7, 48.6, 47.8, 43.6, 36.8, 35.0, 34.0, 33.7, 32.6, 32.2, 30.4, 29.9, 23.3, 18.0.



SI-2-8a: To a solution of **95** (4.0 mg, 9.8 μmmol, 1.0 equiv) in CH_2Cl_2 (0.2 mL), was added propionic anhydride (2 μL, 14.7 μmmol, 1.5 equiv) and TMSOTf (0.75 μL, 4.4 μmmol, 0.45 equiv) successively at 0 °C under Ar. The mixture was stirred at this temperature for 1 h, then quenched with Et_3N, and concentrated *in vacuo*. The resulting residue was purified by PTLC (1:1 EtOAc:hexanes); to afford **SI-2-8a** (4.5 mg, 74%).

Physical state: white foam.

R_f = 0.65 (silica gel, 1:1 EtOAc:hexanes).

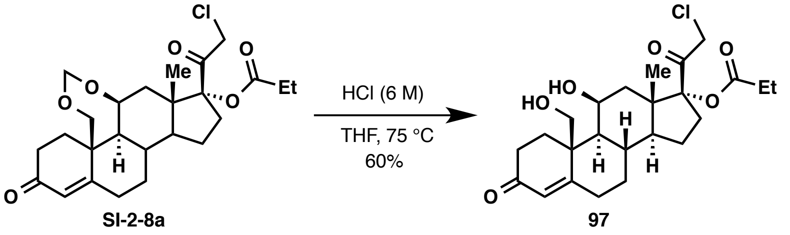
$[\alpha]^{D}_{25}$= +77.5° (c = 0.28, $CHCl_3$).

HRMS (*m/z*): calcd for $C_{25}H_{34}ClO_6$, $[M+H]^+$, 465.2038; found, 465.2039.

IR (film) ν_{max}: 2927, 2861, 1731, 1662, 1127, 1077, 1051.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.85 (s, 1 H), 4.71 (dd, J = 29.0, 4.2 Hz, 2 H), 4.23 (d, J = 15.3 Hz, 1 H), 4.17 (q, J = 3.0 Hz, 1 H), 4.10 (d, J = 15.3 Hz, 1 H), 3.96 (d, J = 12.2 Hz, 1 H), 3.57 (dd, J = 12.2, 1.5 Hz, 1 H), 2.96–2.88 (m, 1H), 2.68 (ddd, J = 13.0, 4.9, 2.6 Hz, 1 H), 2.54 (ddd, J = 17.7, 14.8, 4.9 Hz, 1 H), 2.44–2.31 (m, 5 H), 2.21 (tdd, J = 14.4, 4.5, 2.1 Hz, 1 H), 2.09 (dd, J = 13.6, 3.6 Hz, 1 H), 2.07–2.02 (m, 1 H), 1.92 (dq, J = 11.9, 3.7 Hz, 1 H), 1.86 (dd, J = 13.5, 3.0 Hz, 1 H), 1.82–1.70 (m, 3 H), 1.56–1.52 (m, 1 H), 1.47 (ddt, J = 17.7, 10.8, 5.7 Hz, 1 H), 1.15 (t, J = 7.6 Hz, 3 H), 1.10 (dt, J = 11.2, 1.6 Hz, 1 H), 0.94 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 199.3, 197.6, 174.3, 166.3, 126.7, 94.9, 92.9, 73.4, 64.6, 56.9, 52.3, 47.8, 46.3, 43.6, 37.1, 33.9, 33.7, 32.6, 32.2, 31.4, 30.3, 27.9, 23.5, 17.5, 9.1.



Compound 97: **SI-2-8a** (7.0 mg, 15 μmmol) was dissolved in THF (1.0 mL) and 6 M HCl (0.1 mL), and the solution was heated at 75 °C for 5 h under Ar. The reaction was then cooled to room temperature, and

diluted with EtOAc (3 mL) and brine (3 mL). The mixture was partitioned in a separatory funnel, and the aqueous phase was separated, and extracted with EtOAc (3 x 3 mL). The combined organic phases were dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by PTLC (15:1 CH_2Cl_2:MeOH) to afford **97** (4.1 mg, 60%).

Physical state: white foam.

$\boldsymbol{R_f}$ = 0.20 (silica gel, 1:1 EtOAc:hexanes).

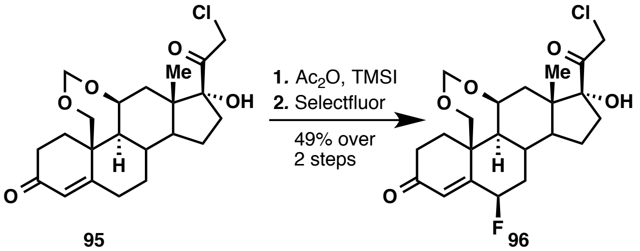
$[\boldsymbol{\alpha}]^{\mathrm{D}}_{25}$= +31.7° ($c$ = 0.24, $CHCl_3$).

HRMS (*m/z*): calcd for $C_{24}H_{34}ClO_6$, $[M+H]^+$, 453.2038; found, 453.2052.

IR (film) $\nu_{\mathbf{max}}$: 2922, 2853, 1732, 1662, 1458, 1191, 1069, 670.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (s, 1 H), 4.47 (q, J = 3.1 Hz, 1 H), 4.30 (d, J = 15.4 Hz, 1 H), 4.13 (d, J = 15.5 Hz, 1 H), 4.12 (d, J = 11.4 Hz, 1 H), 3.60 (d, J = 11.7 Hz, 1 H), 2.94–2.86 (m, 1 H), 2.60 (dd, J = 13.1, 4.5 Hz, 1 H), 2.56–2.45 (m, 1 H), 2.42–2.26 (m, 5 H), 2.16 (ddd, J = 14.9, 12.6, 3.8 Hz, 2 H), 2.08–1.99 (m, 1 H), 1.89–1.75 (m, 3 H), 1.75–1.64 (m, 2 H), 1.49 (td, J = 11.0, 5.7 Hz, 1 H), 1.21 (dt, J = 12.3, 4.4 Hz, 1 H), 1.14 (t, J = 7.5 Hz, 3 H), 0.99 (s, 3 H), 0.92–0.80 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 199.4, 198.0, 174.3, 168.7, 124.0, 94.5, 67.2, 63.7, 56.6, 52.9, 47.0, 46.5, 44.2, 39.1, 34.0, 32.9, 32.3, 31.4, 31.2, 29.9, 27.8, 23.8, 17.5, 9.0.



95 96

Compound 96: To a solution of **95** (200 mg, 0.489 mmol, 1.0 equiv) in Ac_2O (5 mL) was added NaI (293 mg, 1.956 mmol, 4.0 equiv), followed by TMSCl (0.25 mL, 1.956 mmol, 4.0 equiv) at 0 ºC. The resulting mixture was stirred at 0 ºC for 1 h before being diluted with EtOAc (10 mL), and quenched with sat. aq. $Na_2S_2O_3$ (10 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL), and the combined organic phase was washed sequentially with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was used for the next step without further purification.

The resulting oil was dissolved in MeCN (5 mL) and cooled to 0 ºC. Selectfluor® (225 mg, 0.635 mmol, 1.3 equiv) was then added and the resulting mixture was stirred at 0 ºC for 1 h. The reaction was quenched by the addition of H_2O (5 mL), and extracted with EtOAc (3 x 15 mL). The combined organic portions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by column chromatography (1:3 EtOAc:hexanes) to afford **96** (102 mg, 49% over two steps).

Physical state: white solid (m.p. 212–216 ºC).

$\boldsymbol{R_f}$ = 0.44 (silica gel, 2:3 EtOAc:hexanes).

$[\alpha]^{D}_{25}$ = +109.1° (*c* = 0.11, $CHCl_3$).

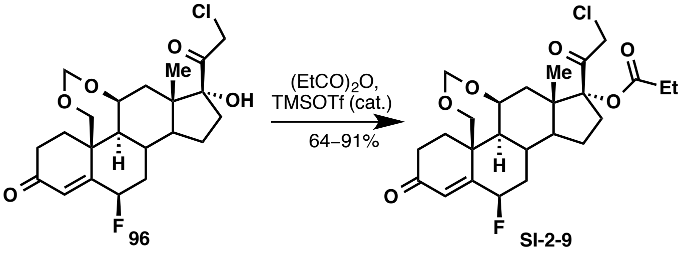
HRMS (*m/z*): calcd for $C_{22}H_{28}ClFO_5$, $[M+H]^+$, 427.1682; found, 427.1681.

IR (film) ν_{max}: 3484, 2945, 1728, 1685, 1666, 1461, 1369, 1230, 1130, 1083, 1052, 918.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.96 (d, *J* = 5.4 Hz, 1 H), 5.00 (d, *J* = 48.8 Hz, 1 H), 4.74 (d, *J* = 4.2 Hz, 1 H), 4.67 (d, *J* = 4.2 Hz, 1 H), 4.61 (d, *J* = 16.4 Hz, 1 H), 4.28 (d, *J* = 16.4 Hz, 1 H), 4.17 (s, 1 H), 4.14 (dd, *J* = 12.7, 3.5 Hz, 1 H), 3.55 (d, *J* = 12.7 Hz, 1 H), 2.91–2.83 (m, 1 H), 2.80–2.73 (m, 1 H), 2.63 (ddd, *J* = 19.2, 14.6, 4.9 Hz, 1 H), 2.48–2.42 (m, 2 H), 2.28 (ddt, *J* = 13.1, 8.1, 3.8 Hz, 1 H), 2.02 (dd, *J* = 13.4, 3.0 Hz, 1 H), 1.88–1.77 (m, 2 H), 1.75 (dd, *J* = 13.4, 3.0 Hz, 1 H), 1.55–1.48 (m, 3 H), 1.36 (dt, *J* = 45.7, 13.7 Hz, 1 H), 1.08 (d, *J* = 11.0 Hz, 1 H), 0.95 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 203.0, 199.8, 176.7, 157.7, 130.7, 92.8, 90.8 (d, *J* = 283.8 Hz), 73.1, 64.6, 55.8, 51.4, 48.7, 47.9, 42.8, 36.7, 35.4 (d, *J* = 22.8 Hz), 34.8, 34.0, 32.4, 26.0, 23.2, 18.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ –169.1.



SI-2-9: To a solution of **96** (12.3 mg, 28.8 µmmol, 1.0 equiv) in CH_2Cl_2 (0.2 mL) was added propionic anhydride (5.5 µL, 43.2 µmmol, 1.5 equiv) and TMSOTf (2 µL, 11.5 µmmol, 0.45 equiv) successively at 0 ºC under Ar. The mixture was stirred for 1 h at the same temperature, then quenched with Et_3N, and concentrated *in vacuo*. The resulting residue was purified by PTLC (2:3 EtOAc:hexanes) to afford **SI-2-9** (12.7 mg, 91%).

Alternatively, **SI-2-9** could be synthesized following this procedure: To a solution of **96** (18.0 mg, 42.2 µmol, 1.0 equiv) in 4:1 CH_2Cl_2:pyridine (1 mL) was added $(EtCO)_2O$ (25 µL, 195.9 µmol, 4.6 equiv) and

DMAP (5.2 mg, 42.2 μmol, 1.0 equiv). The resulting mixture was heated at 40 ºC for 8 h, and then diluted with EtOAc (5 mL) and washed with H_2O (5 mL). The aqueous phase was extracted with EtOAc (2 x 2.5 mL) and the combined organic portions were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by PTLC (2:3 EtOAc:hexanes) to afford **SI-2-9** (13.0 mg, 64%).

Physical state: white foam.

$\boldsymbol{R_f}$ = 0.50 (silica gel, 2:3 EtOAc:hexanes).

$[\alpha]^{D}_{25}$= +49.4° (c = 1.1, $CHCl_3$).

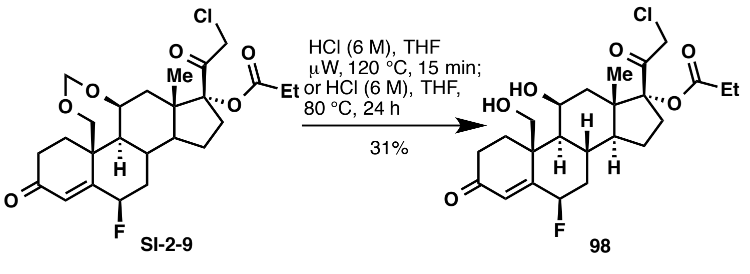
HRMS (*m/z*): calcd for $C_{25}H_{32}ClFO_6$, $[M+H]^+$, 483.1944; found, 483.1941.

IR (film) ν_{max}: 2943, 1732, 1687, 1461, 1368, 1292, 1261, 1228, 1198, 1130, 1055, 919.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.97 (d, J = 5.3 Hz, 1 H), 5.01 (dd, J = 48.8, 2.7 Hz, 1 H), 4.74 (d, J = 4.1 Hz, 1 H), 4.67 (d, J = 4.1 Hz, 1 H), 4.25 (d, J = 15.4 Hz, 1 H), 4.18 (d, J = 3.1 Hz, 1 H), 4.14 (dd, J = 12.7, 3.4 Hz, 1 H), 4.12 (d, J = 15.1 Hz, 1 H), 3.56 (d, J = 12.7 Hz, 1 H), 2.97–2.91 (m, 1 H), 2.82–2.73 (m, 1 H), 2.64 (ddd, J = 19.1, 14.9, 4.9 Hz, 1 H), 2.54–2.42 (m, 2 H), 2.41–2.33 (m, 2 H), 2.28 (ddt, J = 12.9, 8.0, 3.7 Hz, 1 H), 2.09 (dd, J = 13.4, 3.0 Hz, 1 H), 1.88 (dd, J = 13.4, 3.0 Hz, 1 H), 1.82–1.73 (m, 3 H), 1.36 (dt, J = 44.5, 13.9 Hz, 1 H), 1.14 (td, J = 7.6, 1.2 Hz, 3 H), 1.11–1.05 (m, 2 H), 0.96 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 199.6, 197.5, 176.8, 174.2, 157.5, 130.7, 99.7, 93.8 (d, J = 275.6 Hz), 72.9, 64.7, 55.9, 52.2, 47.9, 46.4, 42.8, 37.1, 35.3, 34.0, 32.5, 31.3, 27.9, 26.1, 23.4, 17.4, 9.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ –169.1.



Compound 98: **SI-2-9** (4.0 mg, 8.3 μmmol) was dissolved in THF (1 mL) and 6 M HCl (0.1 mL), and the solution was heated at 80 ºC for 24 h under argon. (Alternatively, the deprotection could be conducted by heating the THF solution of the substrate at 120 ºC under microwave irradiation for 15 min.) The reaction was then cooled to room temperature, and diluted with EtOAc (3 mL) and brine (3 mL). The mixture was partitioned in a separatory funnel, and the aqueous phase was separated, and extracted with EtOAc (3 x 3 mL). The combined organic phases were dried over Na_2SO_4, and

concentrated *in vacuo*. The resulting residue was purified by PTLC (15:1 CH_2Cl_2:MeOH) to afford **98** (1.2 mg, 31%).

Physical state: white foam.

$\boldsymbol{R_f}$ = 0.40 (silica gel, 15:1 CH_2Cl_2:MeOH, run twice).

$[\alpha]_{25}^{D}$ = +27.0° (c = 0.17, $CHCl_3$).

HRMS (*m/z*): calcd for $C_{24}H_{33}ClFO_6$, $[M+H]^+$, 471.1944; found, 471.1951.

IR (film) ν_{max}: 2932, 1729, 1668, 1458, 1272, 1194, 1080, 732.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.15 (d, J = 1.9 Hz, 1 H), 5.30–5.15 (m, 1 H), 4.55 (d, J = 3.0 Hz, 1 H), 4.32 (d, J = 15.2 Hz, 1 H), 4.15 (d, J = 15.2 Hz, 1 H), 3.98 (d, J = 11.7 Hz, 1 H), 3.83 (d, J = 11.8 Hz, 1 H), 2.93 (dd, J = 13.5, 11.0 Hz, 1 H), 2.61 (dd, J = 13.3, 4.6 Hz, 1 H), 2.53 (ddd, J = 18.3, 13.6, 4.8 Hz, 1 H), 2.48–2.35 (m, 5 H), 2.32–2.25 (m, 1 H), 2.23 (dd, J = 14.3, 3.2 Hz, 1 H), 1.91–1.76 (m, 6 H), 1.44–1.34 (m, 1 H), 1.17 (t, J = 7.6 Hz, 3 H), 1.03 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 198.3, 197.8, 174.3, 164.3 (d, J = 11.2 Hz), 119.9 (d, J = 14.0 Hz), 94.2, 87.7 (d, J = 185.7 Hz), 67.1, 65.0, 56.3, 52.9, 47.2, 46.4, 45.1 (d, J = 2.1 Hz), 39.2, 38.2 (d, J = 18.3 Hz), 33.8, 31.2, 31.1, 30.2 (d, J = 11.5 Hz), 27.8, 23.8, 17.5, 9.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ –181.9.

Binding Assay Determination for Analogs

Glucocorticoid receptor (GR) binding assay – biochemical

Glucocorticoid receptor binding was determined by competitive receptor binding assay using the PolarScreen™ Glucocorticoid Receptor Competitor Assay Kit, Green (Life Technologies, catalogue number A15897) in a 384-well format according to the manufacturer's instructions. Briefly, serial dilutions of test and reference compounds were prepared in 384-well plates. Subsequently, the steroidal competitor Fluormone™ GS1 and recombinant glucocorticoid receptor (GR) were added to all wells and the plate was incubated for 2 hours at room temperature and protected from light. Finally, polarization values in each well were determined by reading the plate in an EnVision (Perkin-Elmer) device.

Mineralocorticoid receptor (MR) agonism and antagonism assay – cellular

Agonistic and antagonistic interaction with the mineralocorticoid receptor was determined using the GeneBLAzer® MR DA Assay Kit (Life Technologies, catalogue number K1409) in a 96-well format according to the manufacturer's instructions.

For determination of MR agonistic effect, cells were incubated with 0.14 nM – 1 µM of test compound; the MR agonist aldosterone was included as a positive control in the same concentration range. After 16 h incubation, assay substrate (LiveBLAzer™-FRET B/G) was added to all wells and cells were incubated for 2 h followed by fluorometric detection (409/447 nm excitation and emission wavelength, respectively) of substrate conversion by beta-lactamase.

For determination of MR antagonistic activity, cells were incubated with 0.14 nM – 1 µM of test compound; the MR antagonist spironolactone was included as a positive control in the same concentration range. After 0.5 h, 10 nM of the MR agonist aldosterone was added to all wells and cells were incubated for another 15.5 h at 37° C, 5% CO_2. After that, assay substrate (LiveBLAzer™-FRET B/G) was added to all wells and cells were incubated for 2h followed by fluorometric detection (409/447 nm excitation and emission wavelength, respectively) substrate conversion by beta lactamase.

Interleukin-12B (IL-12B) release from primary human peripheral blood mononuclear cells (PBMC)

The assay was adopted from a previously reported method[4] and is based on mononuclear cells isolated from human blood. Stimulation of these cells with lipopolysaccharide (LPS) induces—among many other processes—the synthesis and secretion of the cytokine IL-12B. Both steroidal (glucocorticoids) and non-steroidal glucocorticoid receptor agonists act anti-inflammatory—e.g., by preventing DNA-binding of inflammatory transcription factors like AP-1 or NFkB—resulting in decreased synthesis/secretion of IL12B. For compound testing, frozen stocks of PBMC were thawed, seeded in 96-well plates (1.2E5 cells/well) and then incubated in RPMI-1640 culture medium with 100 ng/ml LPS for 18 h at 37 °C, 5% CO_2 with or without test compounds (pre-incubation with reference/test compounds for 1h before addition of LPS). Then, IL-12B concentration in the cell culture supernatants was detected by hIL-12B-specific ELISA (Quantikine® human IL-12 p40 Immunoassay, R&D Systems Cat # SP400).

X-Ray Crystallographic Data

Figure S1. X-ray crystallographic structure of **23'** (a bis-ketal derivative of **23**, which was in turn prepared according to the oxidation procedure of estrone reported by Rindone and co-workers[3]).

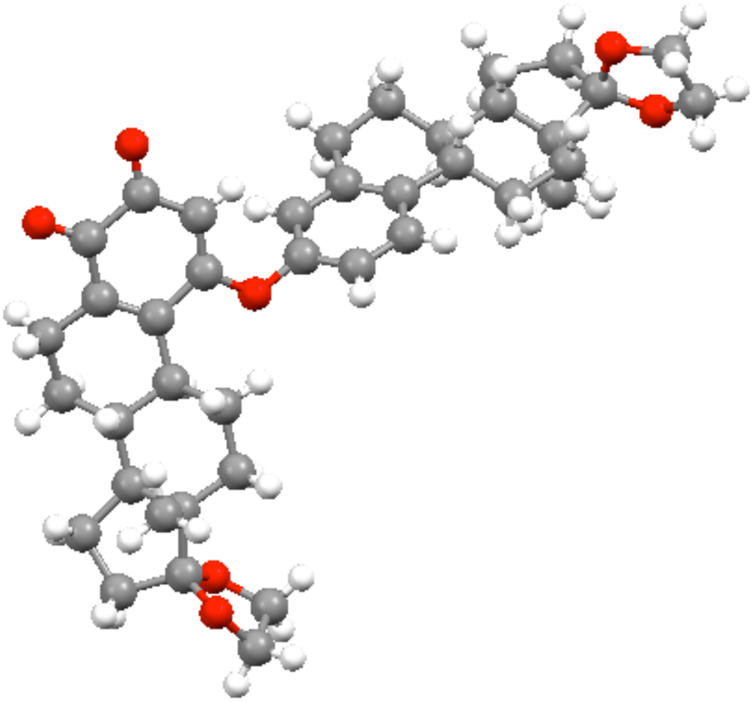


Table S2. Crystal data and structure refinement for **23'**.

Identification code	CCDC 743414	
Empirical formula	C40 H48 O7	
Formula weight	640.78	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.8935(7) Å	α= 90°
	b = 10.0417(8) Å	β= 90°
	c = 36.708(3) Å	γ = 90°
Volume	3278.3(4) $Å^3$	
Z	4	
Density (calculated)	1.298 g/cm^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	1376	
Crystal size	0.40 x 0.30 x 0.08 mm^3	

Crystal color, habit	Orange plate
Theta range for data collection	2.10 to 25.42°
Index ranges	-10<=h<=10, -12<=k<=11, -44<=l<=44
Reflections collected	31138
Independent reflections	6040 [R(int) = 0.0371]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9930 and 0.9658
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6040 / 0 / 424
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0370, wR2 = 0.0913
R indices (all data)	R1 = 0.0406, wR2 = 0.0933
Absolute structure parameter	0.2(8)
Largest diff. peak and hole	0.229 and -0.188 e Å^{-3}

Figure S2. X-ray crystallographic structure of **40**.

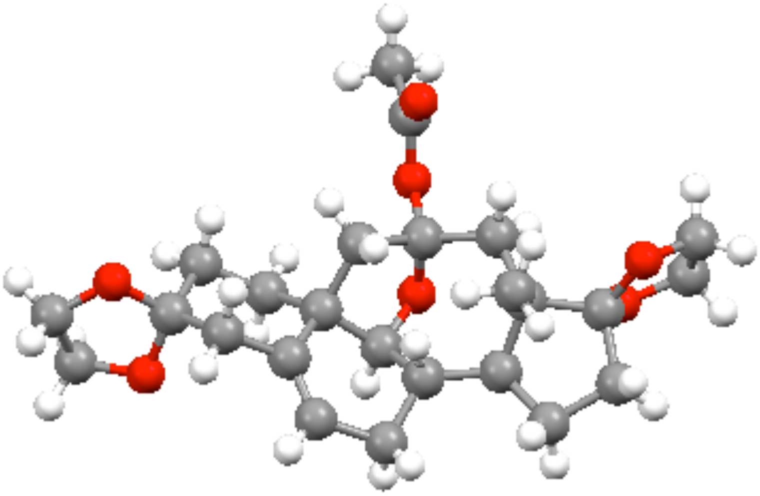


Table S3. Crystal data and structure refinement for **40**.

Identification code	CCDC 1012713
Empirical formula	C25 H34 O7
Formula weight	446.52
Temperature	123(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Space group	P2(1)	
Unit cell dimensions	a = 9.789(2) Å	α= 90°
	b = 7.7354(17) Å	β= 107.521(3)°
	c = 15.707(3) Å	γ = 90°
Volume	1134.2(4) Å^3	
Z	2	
Density (calculated)	1.308 g/cm^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	480	
Crystal size	0.57 x 0.24 x 0.20 mm^3	
Crystal color, habit	Colorless blade	
Theta range for data collection	2.18 to 25.56°	
Index ranges	-11<=h<=11, -9<=k<=9, -18<=l<=18	
Reflections collected	7334	
Independent reflections	3878 [R(int) = 0.0439]	
Completeness to theta = 25.00°	99.7 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9813 and 0.9481	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3878 / 1 / 289	
Goodness-of-fit on F^2	1.125	
Final R indices [I>2sigma(I)]	R1 = 0.0469, wR2 = 0.1148	
R indices (all data)	R1 = 0.0506, wR2 = 0.1187	
Absolute structure parameter	-0.2(10)	
Largest diff. peak and hole	0.314 and -0.381 e Å^{-3}	

Figure S3. X-ray crystallographic structure of **45’**.

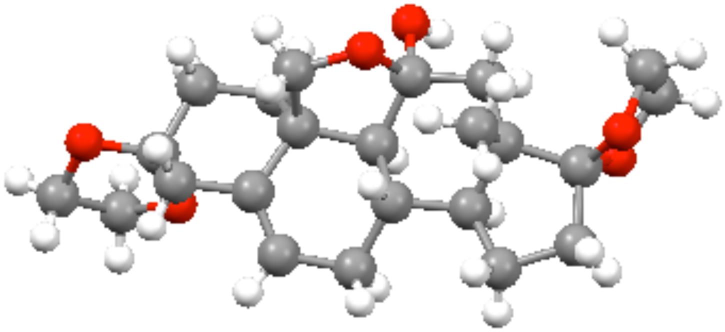


Table S4. Crystal data and structure refinement for **45’**.

Identification code	CCDC 1012711	
Empirical formula	C23 H32 O6	
Formula weight	404.49	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 12.74(2) Å	α= 90°
	b = 6.122(9) Å	β= 92.06(2)°
	c = 13.29(2) Å	γ = 90°
Volume	1036(3) Å^{3}	
Z	2	
Density (calculated)	1.297 g/cm^{3}	
Absorption coefficient	0.093 mm^{-1}	
F(000)	436	
Crystal size	0.33 x 0.20 x 0.08 mm^{3}	
Crystal color, habit	Colorless rod	
Theta range for data collection	1.53 to 25.16°	
Index ranges	-15<=h<=14, -7<=k<=7, -15<=l<=15	
Reflections collected	6692	
Independent reflections	3489 [R(int) = 0.0733]	
Completeness to theta = 25.00°	99.3 %	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least-squares on F^{2}	
Data / restraints / parameters	3489 / 1 / 265	
Goodness-of-fit on F^{2}	1.020	
Final R indices [I>2sigma(I)]	R1 = 0.0693, wR2 = 0.1762	
R indices (all data)	R1 = 0.0748, wR2 = 0.1835	
Absolute structure parameter	-0.1(15)	
Extinction coefficient	0.030(7)	
Largest diff. peak and hole	0.310 and -0.364 e Å^{-3}	

Figure S4. X-ray crystallographic structure of **56**.

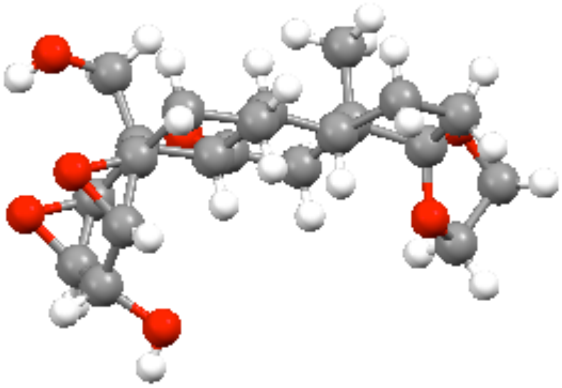


Table S5. Crystal data and structure refinement for **56**.

Identification code	CCDC 1012707	
Empirical formula	C21 H28 O7	
Formula weight	392.43	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.284 Å	α= 90°.
	b = 6.850 Å	β= 100.67°.
	c = 14.331 Å	γ = 90°.
Volume	895.6 Å^3	
Z	2	
Density (calculated)	1.455 Mg/m^3	
Absorption coefficient	0.901 mm^{-1}	
F(000)	420	
Crystal size	0.18 x 0.16 x 0.05 mm^3	
Theta range for data collection	4.85 to 65.51°.	
Index ranges	-10<=h<=10, -7<=k<=7, -16<=l<=16	
Reflections collected	2824	
Independent reflections	2826 [R(int) = 0.0636]	
Completeness to theta = 65.51°	95.4 %	
Absorption correction	Mult-scan	
Max. and min. transmission	0.9563 and 0.8547	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	2826 / 1 / 257
Goodness-of-fit on F^2	1.023
Final R indices [I>2sigma(I)]	R1 = 0.0366, wR2 = 0.0869
R indices (all data)	R1 = 0.0396, wR2 = 0.0887
Absolute structure parameter	-0.2(3)
Largest diff. peak and hole	0.284 and -0.220 e.Å^{-3}

Figure S5. X-ray crystallographic structure of **57**.

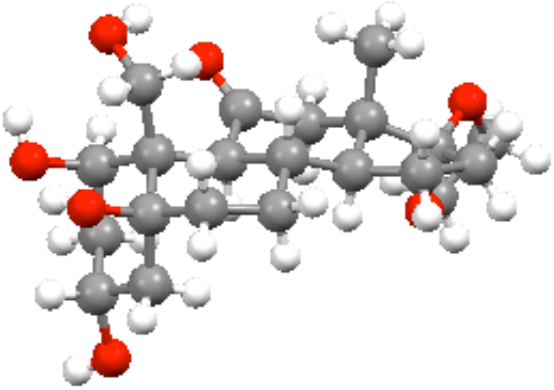


Table S6. Crystal data and structure refinement for **57**.

Identification code	CCDC 1012709	
Empirical formula	C21 H32 O7	
Formula weight	396.47	
Temperature	90(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.5699(6) Å	α= 90°
	b = 6.8599(4) Å	β= 101.480(3)°
	c = 14.4110(8) Å	γ = 90°
Volume	927.13(9) Å^3	
Z	2	
Density (calculated)	1.420 g/cm^3	
Absorption coefficient	0.871 mm^{-1}	
F(000)	428	
Crystal size	0.40 x 0.15 x 0.10 mm^3	
Theta range for data collection	4.71 to 62.15°	

Index ranges	-10<=h<=10, -7<=k<=7, -16<=l<=16
Reflections collected	5354
Independent reflections	2551 [R(int) = 0.0428]
Completeness to theta = 62.15°	99.2 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9180 and 0.7221
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2551 / 1 / 258
Goodness-of-fit on F^2	1.045
Final R indices [I>2sigma(I)]	R1 = 0.0451, wR2 = 0.1193
R indices (all data)	R1 = 0.0460, wR2 = 0.1203
Absolute structure parameter	-0.2(3)
Largest diff. peak and hole	0.243 and -0.237 e Å^{-3}

Figure S6. X-ray crystallographic structure of **64**.

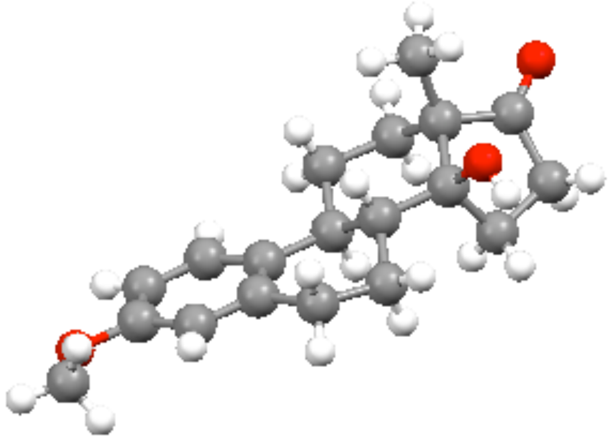


Table S7. Crystal data and structure refinement for **64**.

Identification code	CCDC 1012710	
Empirical formula	C19 H24 O3	
Formula weight	300.38	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.8468(2) Å	α= 90°.
	b = 9.0154(3) Å	β= 90°.

	c = 29.9693(10) Å	γ = 90°.
Volume	1579.72(9) Å^3	
Z	4	
Density (calculated)	1.263 Mg/m^3	
Absorption coefficient	0.667 mm^{-1}	
F(000)	648	
Crystal size	0.22 x 0.18 x 0.12 mm^3	
Crystal color, habit	Colorless Rod	
Theta range for data collection	2.95 to 68.84°.	
Index ranges	-6<=h<=7, -9<=k<=10, -36<=l<=34	
Reflections collected	19481	
Independent reflections	2808 [R(int) = 0.0387]	
Completeness to theta = 65.00°	99.9 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9242 and 0.8671	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2808 / 0 / 202	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0289, wR2 = 0.0689	
R indices (all data)	R1 = 0.0312, wR2 = 0.0705	
Absolute structure parameter	0.12(18)	
Largest diff. peak and hole	0.169 and -0.157 e.Å^{-3}	

Figure S7. X-ray crystallographic structure of **69**.

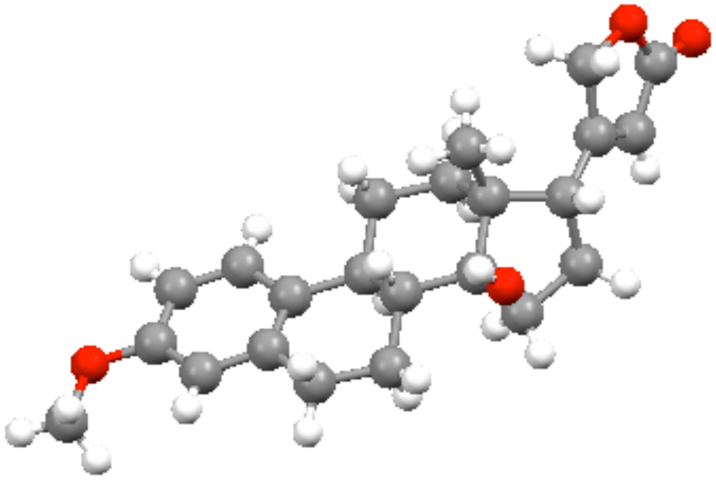


Table S8. Crystal data and structure refinement for **69**.

Identification code	CCDC 1012712	
Empirical formula	C24 H31 O4.50	
Formula weight	391.49	
Temperature	100(2) K	
Wavelength	1.54174 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.1317(3) Å	α= 90°.
	b = 16.5484(7) Å	β= 90°.
	c = 33.6720(14) Å	γ = 90°.
Volume	3973.9(3) Å^3	
Z	8	
Density (calculated)	1.309 Mg/m^3	
Absorption coefficient	0.714 mm^{-1}	
F(000)	1688	
Crystal size	0.47 x 0.15 x 0.08 mm^3	
Crystal color, habit	Colorless Plate	
Theta range for data collection	2.98 to 69.24°.	
Index ranges	-8<=h<=8, -19<=k<=11, -37<=l<=40	
Reflections collected	22612	
Independent reflections	6822 [R(int) = 0.0553]	
Completeness to theta = 65.00°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9451 and 0.7302	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6822 / 0 / 522	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0429, wR2 = 0.1075	
R indices (all data)	R1 = 0.0481, wR2 = 0.1109	
Absolute structure parameter	-0.16(16)	
Extinction coefficient	not measured	
Largest diff. peak and hole	0.303 and -0.225 e.Å^{-3}	

Figure S8. X-ray crystallographic structure of **96**.

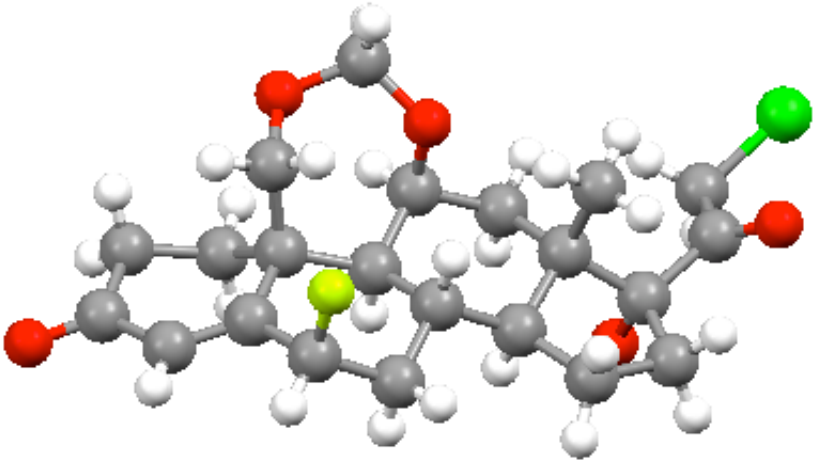


Table S9. Crystal data and structure refinement for **96**.

Identification code	CCDC 1012708	
Empirical formula	C22 H27 Cl F O5	
Formula weight	425.88	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.8008(6) Å	α= 90°.
	b = 11.8602(8) Å	β= 90°.
	c = 21.0411(12) Å	γ = 90°.
Volume	1946.7(2) $Å^3$	
Z	4	
Density (calculated)	1.453 Mg/m^3	
Absorption coefficient	0.239 mm^{-1}	
F(000)	900	
Crystal size	0.350 x 0.300 x 0.250 mm^3	
Theta range for data collection	1.971 to 28.302°.	
Index ranges	-10<=h<=10, -15<=k<=15, -28<=l<=27	
Reflections collected	55228	
Independent reflections	4824 [R(int) = 0.1254]	
Completeness to theta = 25.000°	99.8 %	
Absorption correction	Multi-scan	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4824 / 0 / 263
Goodness-of-fit on F^2	1.084
Final R indices [I>2sigma(I)]	R1 = 0.0457, wR2 = 0.1258
R indices (all data)	R1 = 0.0474, wR2 = 0.1276
Absolute structure parameter	0.00(3) [abs. stereochem. confirmed]
Extinction coefficient	n/a
Largest diff. peak and hole	0.582 and -0.489 e.Å^{-3}

References.

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